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Short Review

RIFM fragrance ingredient safety assessment, [2-(cyclohexyloxy)ethyl] benzene, CAS Registry Number 80858-47-5

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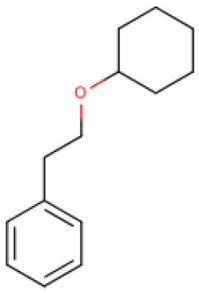
CAS Registry Number: 80858-47-5



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

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 (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative 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.

[2-(Cyclohexyloxy)ethyl]benzene (CAS # 80858-47-5) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that [2-(cyclohexyloxy)ethyl]benzene is not genotoxic. Data from read-across analog (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9) show that [2-(cyclohexyloxy)ethyl]benzene is not expected to present a concern for skin sensitization. The repeated dose and reproductive toxicity endpoints were evaluated using the TTC for a Cramer Class II material, and the exposure to [2-(cyclohexyloxy)ethyl]benzene is below the TTC (0.009 mg/kg/day and 0.009 mg/kg/day, respectively). The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material, and the exposure to [2-(cyclohexyloxy)ethyl]benzene is below the TTC (0.47 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; [2-(cyclohexyloxy)ethyl]benzene is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; [2-(cyclohexyloxy)ethyl]benzene was found not to be a 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, 2017b; Dutta, 2017)

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.

Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: No safety concerns at current, declared use levels. RIFM (1995)

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: Screening-level: 72% day 60 (-OECD 301D) (ECHA Dossier: [2-(cyclohexyloxy)ethyl]benzene; ECHA, 2017)

Bioaccumulation: Screening-level: 456 L/kg (EPI Suite, v4.11; US EPA, 2012a)

Ecotoxicity: 48-h *Daphnia magna* LC50: 0.-636 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: 0.636 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0636 μg/L

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

1. Identification

1. **Chemical Name:** [2-(Cyclohexyloxy)ethyl]benzene
2. **CAS Registry Number:** 80858-47-5
3. **Synonyms:** Benzene, [2-(cyclohexyloxy)ethyl]-; Phenafleur; [2-(Cyclohexyloxy)ethyl]benzene
4. **Molecular Formula:** $C_{14}H_{20}O$
5. **Molecular Weight:** 204.13
6. **RIFM Number:** 5995
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 288.64 °C (US EPA, 2012a)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 4.54 (US EPA, 2012a)
4. **Melting Point**: 42.64 °C (US EPA, 2012a)
5. **Water Solubility:** 5.566 mg/L (US EPA, 2012a)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00246 mm Hg @ 25 °C (US EPA, 2012a), 0.00135 mm Hg @ 20 °C (US EPA, 2012a)
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:** Floral, hyacinth, green, metallic,

fruity, raspberry, balsam

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.50% (RIFM, 2017a)
3. **Inhalation Exposure*:** 0.0010 mg/kg/day or 0.073 mg/day (RIFM, 2017a)
4. **Total Systemic Exposure**:** 0.0079 mg/kg/day (RIFM, 2017a)

*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 4. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** 80%

Data from RIFM's *in silico* skin absorption model (RIFM, 2014) were used to predict the dermal penetration of 80% for [2-(cyclohexyloxy)ethyl]benzene as shown below.

	Chemical Name
Name	[2-(Cyclohexyloxy)ethyl]benzene
J_{max} (μg/cm^2/h)	18.486[1]
Skin Absorption Class	80%

[1] J_{max} was calculated based on measured log K_{ow} = 3.99 (RIFM, 2014) and water solubility = 202.2 mg/L (RIFM, 2014).

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9)
   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.

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

[2-(Cyclohexyloxy)ethyl]benzene 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

Available; accessed 07/27/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, [2-(cyclohexyloxy)ethyl]benzene does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. [2-(Cyclohexyloxy)ethyl]benzene was assessed in the BlueScreen assay and found negative for both genotoxicity, with and without metabolic activation (RIFM, 2013). The mutagenic activity of [2-(cyclohexyloxy)ethyl]benzene has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with [2-(cyclohexyloxy)ethyl]benzene 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, 2017b). Under the conditions of the study, [2-(cyclohexyloxy)ethyl]benzene was not mutagenic in the Ames test.

The clastogenic activity of [2-(cyclohexyloxy)ethyl]benzene was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with [2-(cyclohexyloxy)ethyl]benzene in DMSO at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Micronuclei analysis was conducted up to doses producing appropriate cytotoxicity (90 μg/mL) in all the test conditions. [2-(Cyclohexyloxy)ethyl]benzene did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (Dutta, 2017). Under the conditions of the study, [2-(cyclohexyloxy)ethyl]benzene was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, [2-(cyclohexyloxy)ethyl]benzene does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/28/2017.

10.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on [2-(cyclohexyloxy)ethyl]benzene or any read-across materials. The total systemic exposure to [2-(cyclohexyloxy)ethyl]benzene is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on [2-(cyclohexyloxy)ethyl]benzene or on any read-across materials that can be used to support the repeated dose toxicity endpoint. When correcting for skin absorption (see Section 4), the total systemic exposure to [2-(cyclohexyloxy)ethyl]benzene (7.9 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/28/17.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on [2-(cyclohexyloxy)ethyl]benzene or any read-across materials. The total systemic exposure to [2-(cyclohexyloxy)ethyl]benzene is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on [2-(cyclohexyloxy)ethyl]benzene or any read-across materials that can be used to support the reproductive toxicity endpoint. When correcting for skin absorption (see Section 4), the total systemic exposure to [2-(cyclohexyloxy)ethyl]benzene (7.9 μg/kg bw/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/28/17.

10.1.4. Skin sensitization

Based on the existing data and read-across material (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9), [2-(cyclohexyloxy)ethyl]benzene does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for [2-(cyclohexyloxy)ethyl]benzene. Based on the existing data and read-across material (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9; see Section 5), [2-(cyclohexyloxy)ethyl]benzene does not present a concern for skin sensitization. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In guinea pigs, a Buehler test with [2-(cyclohexyloxy)ethyl]benzene did not present reactions indicative of sensitization (RIFM, 1981b). Additionally, a guinea pig maximization test with 100% read-across material (3-methoxy-2-methylpropyl)benzene did not present reactions indicative of sensitization (RIFM, 1995). In a confirmatory human repeat insult patch test (HRIPT) with 11480 μg/cm^2 of [2-(cyclohexyloxy)ethyl]benzene, no reactions indicative of sensitization were observed in any of the 47 volunteers (RIFM, 1981a). In another HRIPT with 7500 μg/cm^2 of [2-(cyclohexyloxy)ethyl]benzene, no reactions indicative of sensitization were observed in any of the 51 volunteers (RIFM, 1982).

Based on weight of evidence from structural analysis, animal and human studies, and read-across material (3-methoxy-2-methylpropyl) benzene, [2-(cyclohexyloxy)ethyl]benzene does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/31/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, [2-(cyclohexyloxy)ethyl]benzene 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 [2-(cyclohexyloxy)ethyl]benzene 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 lack of absorbance, [2-(cyclohexyloxy)ethyl]benzene 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} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/12/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level of material [2-(cyclohexyloxy)ethyl]benzene 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 [2-(cyclohexyloxy)ethyl]benzene. Based on the Creme RIFM Model, the inhalation exposure is 0.073 mg/day. This exposure is 6.4 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/1/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of [2-(cyclohexyloxy)ethyl]benzene 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, [2-(cyclohexyloxy)ethyl]benzene 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 [2-(cyclohexyloxy)ethyl]benzene as being either 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 ≥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), [2-(cyclohexyloxy)ethyl]benzene presents a risk to the aquatic compartment in the screening-level assessment.

10.3. Key studies

10.3.1. Biodegradation

No data available.

10.3.2. Ecotoxicity

No data available.

10.3.2.1. Other available data. [2-(Cyclohexyloxy)ethyl]benzene has been registered under REACH, and the following data is available (ECHA, 2017):

A prolonged ready biodegradability test was conducted according to the OECD 301D method. Under the conditions of the study, biodegradation of 33% and 72% was observed after 28 and 60 days, respectively.

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be 0.39 mg/L.

10.3.2.2. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.54	4.54
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 additional assessment is necessary.

The RIFM PNEC is 0.0636 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/29/17.

11. Literature Search*

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.697			1,000,000	0.001697	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.887	0.636	1.248	10,000	0.0636	Neutral Organics

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 07/27/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110636.

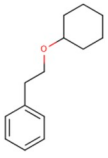
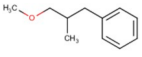
Appendix

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 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 (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 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	[2-(Cyclohexyloxy)ethyl]benzene	(3-Methoxy-2-methylpropyl)benzene
CAS No.	80858-47-5	120811-92-9
Structure		
Similarity (Tanimoto Score)		0.51
Read-across Endpoint		• Skin sensitization
Molecular Formula	$C_{14}H1_{20}O$	$C_{11}H1_{16}O$
Molecular Weight	204.31	164.25
Melting Point (°C, EPI Suite)	42.64	−5.78
Boiling Point (°C, EPI Suite)	288.64	219.02
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.328	18.4
Log Kow (KOWWIN v1.68 in EPI Suite)	4.54	3.17
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.566	127.3
J_{max} (μg/cm^2/h, SAM)	18.486	126.773
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.68E-004	1.63E-004
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found

Protein Binding Potency	• 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	• No alert found
Metabolites		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on [2-(cyclohexyloxy)ethyl]benzene (CAS # 80858-47-5). 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, (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- (3-Methoxy-2-methylpropyl)benzene (CAS # 120811-92-9) was used as a read-across analog for the target material [2-(cyclohexyloxy)ethyl] benzene (CAS # 80858-47-5) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic ethers.
  - o The target substance and the read-across analog share similar alkylphenyl ether structures.
  - o The key structural difference between the target substance and the read-across analog is the target substance is an ethylphenyl ether with a cyclohexyl substituent whereas the read-across analog is a methylpropylphenyl ether with a methyl substituent. These structural differences are toxicologically insignificant.
  - o Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these alkylphenyl ether structures. 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 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.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Dutta, A., 2017. [2-(Cyclohexyloxy)ethyl]benzene: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). (Unpublished).

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. European Chemical Agency Read-Across Assessment Framework. ECHA Read-Across Assessment Framework. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

ECHA, 2017. [2-(cyclohexyloxy)ethyl]benzene Registration Dossier. Retrieved from. https://www.echa.europa.eu/lv/web/guest/registration-dossier/-/registered-dossier/19515.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

OECD, 2012. The OECD QSAR Toolbox, V 3.4. http://www.qsartoolbox.org/.

OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1981. Repeated Insult Patch Test of 6,7-Dihyrdo-1,1,2,3,3-Pentamethyl-4(5h)-Indanone in Human Subjects. Unpublished report from International Flavors and Fragrances. RIFM report number 19905. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1981. Delayed Contact Hypersensitivity Study in guinea Pigs with [2-(cyclohexyloxy)ethyl]benzene. Unpublished report from International Flavors and Fragrances. RIFM report number 52060. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Evaluation of Fragrance Materials by Dermal Contact in Human Subjects. Unpublished report from International Flavors and Fragrances. RIFM report number 51299. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1995. Benzene, (3-Methoxy-2-Methylpropyl)-: Skin Sensitisation Study in the guinea Pig. Unpublished report from Firmenich SA. RIFM report number 38893. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of [2-(cyclohexyloxy)ethyl]benzene in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65730. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014. An in Silico Skin Absorption Model for Fragrance Materials. RIFM report number 67839. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Expo. Surv. 16 May 2017.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. [2-(Cyclohexyloxy)ethyl] benzene: Bacterial Reverse Mutation Assay. RIFM report number 71519. RIFM, Woodcliff Lake, NJ, USA.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme

RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
US EPA, 2012. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.