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RIFM fragrance ingredient safety assessment, cyclohexaneethyl acetate, CAS Registry Number 21722-83-8

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Name: Cyclohexaneethyl acetate CAS
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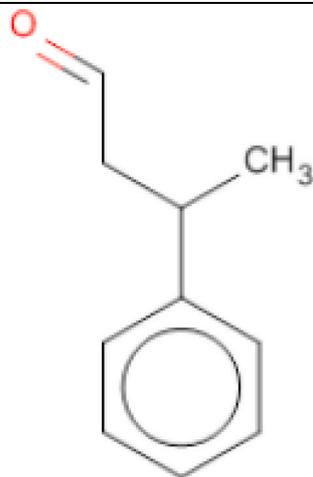
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**Abbreviation/Definition List:**

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017; Safford et al., 2015; Safford et al., 2017; Safford et al., 2017) compared to a deterministic aggregate approach

DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

DRF - Dose Range Finding

DST - Dermal Sensitization Threshold

ECHA - European Chemicals Agency

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

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

QSAR - Quantitative Structure-Activity Relationship

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

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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.

Cyclohexaneethyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cyclohexaneethyl acetate is not 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 cyclohexaneethyl acetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across material octahydro-4,7-methano-1H-indenemethyl acetate (CAS # 30772-69-1) show that there are no safety concerns for cyclohexaneethyl acetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; cyclohexaneethyl acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cyclohexaneethyl acetate 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., PEC/PNEC [Predicted Environmental Concentration/Predicted No Effect Concentration]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2019; RIFM, 2020)

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

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

Skin Sensitization: Not a concern (RIFM, 1991a; RIFM, 1991b) for skin sensitization under the current, declared levels of use.

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: 2.96 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:

Screening-level: 114.5 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: 96-h algae EC50: 1.471 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; Salvitto et al., 2002)

Critical Ecotoxicity Endpoint: 96-h algae EC50: 1.471 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.147 µg/L

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

1. Identification

- 1. Chemical Name:** Cyclohexaneethyl acetate
- 2. CAS Registry Number:** 21722-83-8
- 3. Synonyms:** Cyclohexylethyl acetate; 2-Cyclohexylethyl acetate; Hexahydrophenethyl acetate; アルキル (C = 1 ~ 4) カルボン酸 □クロヘキシルエチル; Cyclohexaneethyl acetate
- 4. Molecular Formula:** C₁₀H₁₈O₂
- 5. Molecular Weight:** 170.25
- 6. RIFM Number:** 538
- 7. Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

- Boiling Point:** 58–60 °C (Katz, 1955a), >200 °C (FMA), 219.25 °C (EPI Suite)
- Flash Point:** 79 °C (GHS), 175°F; CC (FMA)
- Log Kow:** 3.62 (EPI Suite)
- Melting Point:** -3.31 °C (EPI Suite)
- Water Solubility:** 49.2 mg/L (EPI Suite)
- Specific Gravity:** Not Available
- Vapor Pressure:** 0.0899 mm Hg @ 20 °C (EPI Suite v4.0), 0.136 mm Hg @ 25 °C (EPI Suite)
- UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ · cm⁻¹)
- Appearance/Organoleptic:** A colorless oily liquid

3. Volume of use (worldwide band)

- 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

- 95th Percentile Concentration in Hydroalcohols:** 0.02% (RIFM, 2017)
- Inhalation Exposure*:** 0.00081 mg/kg/day or 0.057 mg/day (RIFM, 2017)
- Total Systemic Exposure**:** 0.0024 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 V. 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).

5. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- Inhalation:** Assumed 100%

6. 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:

- Genotoxicity:** None
 - Repeated Dose Toxicity:** None
 - Reproductive Toxicity:** None
 - Skin Sensitization:** Octahydro-4,7-methano-1H-indenemethyl acetate (CAS # 30772-69-1)
 - Phototoxicity/Photoallergenicity:** None
 - Local Respiratory Toxicity:** None
 - Environmental Toxicity:** None
- Read-across Justification: See Appendix below

7. Metabolism

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

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

Cyclohexaneethyl acetate is reported to occur in the following foods by the VCF*:

- Beli, bael (*Aegle marmelos* Correa).
- Passion fruit (*Passiflora* species).

*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.

9. REACH dossier

“<https://echa.europa.eu/registration-dossier/-/registered-dossier/27073>” \o “<https://echa.europa.eu/registration-dossier/-/registered-dossier/27073>” Available; accessed 05/03/19 (ECHA, 2019).

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, cyclohexaneethyl acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of cyclohexaneethyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* strain WP2uvrA were treated with cyclohexaneethyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 µg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2019). Under the conditions of the study, cyclohexaneethyl acetate was not mutagenic in the Ames test.

The clastogenic activity of cyclohexaneethyl acetate 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 cyclohexaneethyl acetate in DMSO at concentrations up to 1702 µg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. Cyclohexaneethyl acetate did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2020). Under the conditions of the study, cyclohexaneethyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

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

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on cyclohexaneethyl acetate or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to cyclohexaneethyl acetate (2.4 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) 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: 05/14/19.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on cyclohexaneethyl acetate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to cyclohexaneethyl acetate (2.4 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: 05/07/19.

11.1.4. Skin sensitization

Based on the existing data and read-across material octahydro-4,7-methano-1H-indenemethyl acetate (CAS # 30772-69-1), cyclohexaneethyl acetate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for cyclohexaneethyl acetate. Based on the existing data and read-across material octahydro-4,7-methano-1H-indenemethyl acetate (CAS # 30772-69-1; see Section VI), cyclohexaneethyl acetate does not present a concern for skin sensitization under the current, declared levels of use. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD toolbox v 4.2). In guinea pigs, maximization tests with read-across material octahydro-4,7-methano-1H-indenemethyl acetate did not present reactions indicative of sensitization (RIFM, 1991a; RIFM, 1991b). In a human maximization test, no skin sensitization reactions were observed with 4% cyclohexaneethyl acetate (RIFM, 1974). In a confirmatory human repeat insult patch test (HRIPT) with 2500 µg/cm² of octahydro-4,7-methano-1H-indenemethyl acetate in petrolatum, no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1976). Additionally, in another confirmatory HRIPT with 3876 µg/cm² of octahydro-4,7-methano-1H-indenemethyl acetate in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 42 volunteers (RIFM, 1972).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material octahydro-4,7-methano-1H-indenemethyl acetate, cyclohexaneethyl acetate 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: 05/09/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, cyclohexaneethyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for cyclohexaneethyl acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, cyclohexaneethyl acetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. 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: 05/06/19.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on cyclohexaneethyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.057 mg/day. This exposure is 24.6 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/09/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cyclohexaneethyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, cyclohexaneethyl acetate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA,

2012a) did not identify cyclohexaneethyl acetate 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, 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.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), cyclohexaneethyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. *Biodegradation.* No data available.

11.2.1.2.2. *Ecotoxicity.* No data available.

11.2.1.2.3. *Other available data.* Cyclohexaneethyl acetate has been registered for REACH with following additional data available (ECHA, 2019):

A *Daphnia* acute immobilization test was conducted according to OECD 202 guidelines under static conditions. The 48-h EC50 value was reported to be 36.82 mg/L (95% CI: 30.08–45.07 mg/L).

An algae growth inhibition test was conducted according to OECD 201 guidelines under static conditions. The 72-h EC50 value, based on the growth rate, was reported to be 126.59 mg/L (95% CI: 102.48–156.38 mg/L).

11.2.2. Risk assessment refinement

Cyclohexaneethyl acetate has passed the screening criteria; measured data is included for completeness and has not been used in PNEC derivation.

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$).

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	3.62	3.62
Biodegradation Factor Used	1	1
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 0.147 $\mu\text{g/L}$. 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: 06/14/19.

12. 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>
- **National Library of Medicine's Toxicology Information Services:** <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/opthpv/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 09/30/19.

Declaration of competing interest

The authors declare that they have no known competing financial

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ($\mu\text{g/L}$)	Chemical Class
RIFM Framework Screening-level (Tier 1)	244.2			1,000,000	0.2442	

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.2020.111656>.

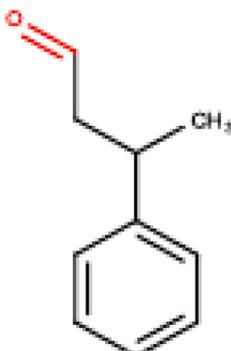
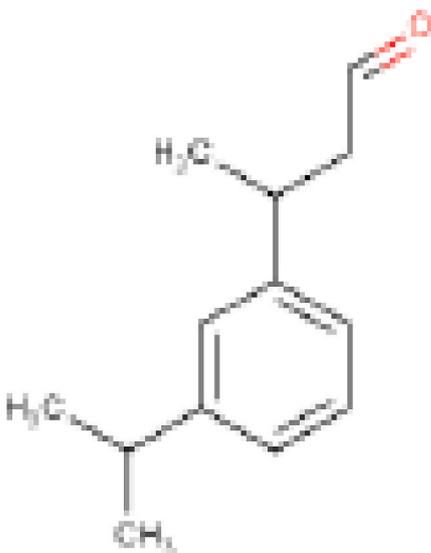
Appendix

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).
- 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 and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Cyclohexaneethyl acetate	Octahydro-4,7-methano-1H-indenemethyl acetate
CAS No.	21722-83-8	30772-69-1
Structure		
Similarity (Tanimoto Score)		0.79
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_{10}H_{18}O_2$	$C_{13}H_{20}O_2$
Molecular Weight	170.25	208.30
Melting Point (°C, EPI Suite)	-3.31	44.24
Boiling Point (°C, EPI Suite)	219.25	265.26
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.81E+01	1.08E+00

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(continued)

	Target Material	Read-across Material
Log K _{OW} (KOWWIN v1.68 in EPI Suite)	3.62	3.55
Water Solubility (mg/L, @ 25° C, WSKOW v1.42 in EPI Suite)	49.2	36.64
J _{max} (µg/cm ² /h, SAM)	38.971	12.285
Henry's Law (Pa·m ³ /mol, Bond Method, EPI Suite)	5.69E+01	2.59E+01
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 according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
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
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 cyclohexaneethyl acetate (CAS # 21722-83-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism simulation, physical–chemical properties, and expert judgment, octahydro-4,7-methano-1H-indenemethyl acetate (CAS # 30772-69-1) was identified as a read-across analog with sufficient data for toxicological evaluation.

- Octahydro-4,7-methano-1H-indenemethyl acetate (CAS # 30772-69-1) was used as a read-across analog for the target material cyclohexaneethyl acetate (CAS # 21722-83-8) for the skin sensitization endpoint.
 - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic cyclic esters.
 - o The target substance and the read-across analog share a primary aliphatic cyclic alcohol moiety in the ester functionality.
 - o The key difference between the target substance and the read-across analog is that the read-across analog is the acetate ester of a fused bridged cyclic alcohol, whereas the target substance is the acetate ester of a primary alcohol. This structural difference is toxicologically insignificant for the skin sensitization endpoint.
 - o The 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 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 There are no toxicological alerts for the target substance as well as for the read-across analog. Data are consistent with *in silico* alerts.
 - 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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