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Short Review

RIFM fragrance ingredient safety assessment, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R), CAS Registry Number 1378867-81-2

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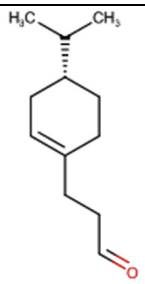
Name: 1-Cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R)

CAS Registry Number: 1378867-81-2



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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020).
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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 Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
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, 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,

(*continued on next column*)

(*continued*)

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.

1-Cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) 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 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog β,4-dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0) provided 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) a No Expected Sensitization Induction Level (NESIL) of 5500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra for read-across analog β,4-dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0); 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) 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 genotoxic. (RIFM, 2013b; RIFM, 2016c)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: NESIL = 5500 μg/cm^2. RIFM (2006)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Critical Measured Value: 63% (OECD 310) Headspace test — RIFM (2013b)

Bioaccumulation:
Screening-level: 333 L/kg — (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 2.43 mg/L — (RIFM Framework; Salvito, 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 2.43 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.00243 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 1-Cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R)
2. **CAS Registry Number:** 1378867-81-2
3. **Synonyms:** Lilybelle; 1-Cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R)
4. **Molecular Formula:** $C_{12}H_{20}O$
5. **Molecular Weight:** 180.29
6. **RIFM Number:** 1222

7. **Stereochemistry:** 4R enantiomer specified. One chiral center present, and 2 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 215.5–250.5 °C at atmospheric pressure of 1013.25 hPa (RIFM, 2013d)
2. **Flash Point:** 118.0 °C (corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2013e)
3. **Log K_{OW}:** 4.3 (RIFM, 2012c), 4.3 (RIFM, 2013a)
4. **Melting Point**: No freezing point down to −75 °C at atmospheric pressure of 1013.25 hPa (RIFM, 2013d)
5. **Water Solubility:** Not Available
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** Not Available
8. **UV Spectra:** Not Available
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.21% (RIFM, 2017a)
2. **Inhalation Exposure*:** 0.0000072 mg/kg/day or 0.00049 mg/day (RIFM, 2017a)
3. **Total Systemic Exposure**:** 0.0044 mg/kg/day (RIFM, 2017a)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015, 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, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs **Selected**:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** β,4-Dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0)
   e. **Phototoxicity/Photoallergenicity:** β,4-Dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0)
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. 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)

1-Cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) is not reported to occur in foods 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.

9. REACH dossier

Available; accessed 06/22/20 (ECHA, 2014).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.42
2	Products applied to the axillae	0.13
3	Products applied to the face/body using fingertips	2.5
4	Products related to fine fragrances	2.4
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.60
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.60
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.60
5D	Baby cream, oil, talc	0.60
6	Products with oral and lip exposure	1.4
7	Products applied to the hair with some hand contact	4.8
8	Products with significant ano-genital exposure (tampon)	0.25
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.6
10A	Household care products with mostly hand contact (hand dishwashing detergent)	17
10B	Aerosol air freshener	17
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	9.2
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R), the basis was the skin sensitization NESIL of 5500 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2uvrA were treated with 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) 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, 2013b). Under the conditions of the study, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) was not mutagenic in the Ames test.

The clastogenic activity of 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) 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 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) in acetone at concentrations up to 1875 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1875 μg/mL in the presence and absence of metabolic activation. 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2016c). Under the conditions of the study, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) was considered to be non-clastogenic in the in vitro micronucleus test.

Based on the data available, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/21/20.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R), or any read-across materials. The total systemic exposure to 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) 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 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (4.4 μg/kg/day) is below the TTC for 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) (30 μg/kg/day; Kroes, 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R), or any read-across materials. The total systemic exposure to 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) 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 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R), or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (4.4 μg/kg/day) is below the TTC for 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/31/20.

11.1.4. Skin sensitization

Based on the existing data and read-across β,4-dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0), 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) is considered a skin sensitizer with a defined NESIL of 5500 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R). Based on the existing data and read-across material β,4-dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0; see Section VI), 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) is considered a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, β,4-dimethylcyclohex-3-ene-1-propan-1-al, was found to be negative in an in vitro direct peptide reactivity assay (DPRA) but positive in KeratinoSens and the human Cell Line Activation Test (h-CLAT) test (RIFM, 2016a; RIFM, 2016b; RIFM, 2017c). In a murine local lymph node assay (LLNA), 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) was found to be sensitizing with an EC3 value of 17% (4250 μg/cm^2) (ECHA, 2014; RIFM, 2012a). In 2 other murine LLNAs, read-across material β,4-dimethylcyclohex-3-ene-1-propan-1-al was found to be sensitizing with EC3 values of 8.1% (2025 μg/cm^2) and 37.3% (9325 μg/cm^2) (RIFM, 2005a; RIFM, 2005b). However, in another LLNA study, read-across material β,4-dimethylcyclohex-3-ene-1-propan-1-al was not found to be sensitizing up to 50% (RIFM, 2012b). In a guinea pig Buehler test, the read-across material β,4-dimethylcyclohex-3-ene-1-propan-1-al presented reactions indicative of sensitization when 25% was used for induction (RIFM, 1991). Additionally, in a Confirmation of No Induction in Humans test (CNIH), the target material, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R), stabilized with vitamin E in an unspecified vehicle did not lead to induction of skin sensitization in any of the 104 volunteers. Data on 3 CNIHs conducted with the read-across material were available. In a CNIH with 10%, or 5510 μg/cm^2 of the read-across material β,4-dimethylcyclohex-3-ene-1-propan-1-al in 3:1 DEP:EtOH, stabilized with 0.1% BHT, no skin sensitization reactions were observed in 105 volunteers (RIFM, 2006). However, in another CNIH with 10% or 5510 μg/cm^2 of read-across material, stabilized with 0.1% tocopherol (vehicle was not reported), reactions indicative of sensitization were observed in 3/102 volunteers (RIFM, 2008). Another CNIH with the read-across material stabilized with 0.1% tocopherol at a lower concentration of 2.2% or 2598 μg/cm^2 did not lead to induction of skin sensitization in any of the 110 volunteers (RIFM, 2018.)

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and data on the read-across material β.,4-dimethylcyclohex-3-ene-1-propan-1-al, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) is a sensitizer with a WoE NESIL of 5500 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b).

Additional References: RIFM, 2017b.

Literature Search and Risk Assessment Completed On: 08/17/20.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorbance spectra for the structurally related

Table 1
Data Summary for β,4-dimethylcyclohex-3-ene-1-propan-1-al as read-across material for 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R).

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
5675 (2)	Weak	5510	NA	5510	5500

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

material, β,4-dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0), 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) 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 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) in experimental models. UV/Vis absorption spectra are not available for the target material, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R). UV/Vis absorption spectra for the structural analog, β,4-dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0), 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, 2009). Based on the lack of absorbance for the structurally related analog, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra were not available for the target material, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R). UV/Vis absorption spectra for the structural analog, β,4-dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0), 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/10/20.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The exposure level for 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) 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 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R). Based on the Creme RIFM Model, the inhalation exposure is 0.00049 mg/day. This exposure is 2857.14 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/29/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 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), 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Biodegradation. **RIFM, 2013f:** The ready biodegradability of the test material was evaluated using the Headspace test according to the OECD 310 guideline. Biodegradation of 63% (95% CI: 52%–74%) was observed after 28 days.

11.2.2. Ecotoxicity

RIFM, 2013a: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 value based on nominal test concentrations was reported to be 0.801 mg/L (95% CI: 0.673–0.952).

RIFM, 2015: The acute fish (*Dania rerio*) toxicity test was conducted according to the OECD 203 guideline under semi-static conditions. The 96-h LC50 value based on mean measured concentration was reported to

be 1.41 mg/L (95% CI: 0.832–3.274 mg/L).

RIFM, 2013c: The algae inhibition test was conducted according to the OECD 201 guideline in a closed vessel system under static conditions. The 96-h EC50 values for growth rate and yield based on mean measured concentrations were reported to be 6.65 mg/L (95% CI: 5.83–8.57 mg/L) and 6.04 mg/L, respectively.

11.2.3. Other available data

1-Cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) has been registered for REACH with the following additional data available at this time (ECHA, 2014):

The 21-day *Daphnia magna* reproduction test was conducted according to the OECD 211 guideline under semi-static conditions. The 21-day NOEC values based on mean measured concentrations were reported to be 0.482 mg/L and 0.0252 mg/L, respectively.

11.2.3.1. 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)**	2.43			1000000	0.00243	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	4.3	4.3
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	No VoU
Risk Characterization: PEC/PNEC	**<1**	**NA**

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.00243 μg/L. The revised PEC/PNECs for EU and NA (No VoU) are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 07/24/20.

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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **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/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/13/21.

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.2021.112612.

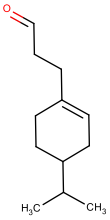
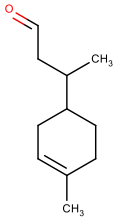
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017).

- 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020), 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, 2020).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of the alert system.

	Target Material	Read-across Material
Principal Name	1-Cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R)	β,4-Dimethylcyclohex-3-ene-1-propan-1-al
CAS No.	1378867-81-2	6784-13-0
Structure		
Similarity (Tanimoto Score)		0.85
Endpoint		Skin sensitization Phototoxicity
Molecular Formula	$C_{12}H_{20}O$	$C_{11}H_{18}O$
Molecular Weight	180.291	166.264
Melting Point (°C, EPI Suite)	16.10	5.24
Boiling Point (°C, EPI Suite)	250.66	232.75
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.51E+00	9.03E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.11E+01	3.39E+01
Log K_{OW}	4.33	3.84
J_{max} (μg/cm^2/h, SAM)	1.64	4.53
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.35E+01	4.03E+01
Skin Sensitization		
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Protein Binding (OECD)	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls
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)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.	Alert for Schiff base formation identified.
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 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) (CAS # 1378867-81-2). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, β,4-dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- β,4-Dimethylcyclohex-3-ene-1-propan-1-al (CAS # 6784-13-0) was used as a read-across analog for the target material 1-cyclohexene-1-propanal, 4-(1-methylethyl)-, (4R) (CAS # 1378867-81-2) for the skin sensitization and phototoxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to a class of terpene carbaldehydes.
  - o The target substance and the read-across analog share an aldehyde with an alkyl-cyclic hydrocarbon fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has isopropyl substitution, while the read-across analog has methyl substitution on the cyclic hydrocarbon fragment. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - 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 a 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 The target substance and the read-across analog have Schiff base formation alerts for the skin sensitization endpoint. This alert is due to the presence of an aldehyde functional group. The data on the read-across analog confirm that the read-across analog does not pose a concern for skin sensitization. Therefore, based on the data for the read-across analog and the structural similarity between the target substance and the read-across analog, the predicted alerts are superseded by data.
  - o The target material and the read-across analog do not have a chromophore that is expected to absorb in the UV/Vis range of the electromagnetic spectrum that is of interest to human health toxicity. The data on the read-across analog confirm that the substance does not absorb in the UV/Vis range. Therefore, the structural difference between the target material and the read-across analog is toxicologically insignificant for the phototoxicity endpoint, and the target material can be predicted to not absorb in the UV/Vis range.
  - 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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