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RIFM fragrance ingredient safety assessment, allyl cyclohexanepropionate, CAS Registry Number 2705-87-5

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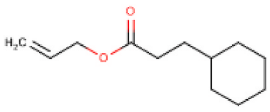

Abbreviation/Definition List:

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

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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.,

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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 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
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, 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.

Allyl cyclohexanepropionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that allyl cyclohexanepropionate is not genotoxic and provide a calculated margin of exposure (MOE) > 100 for the reproductive toxicity endpoint. Data on read-across material allyl (cyclohexyloxy)acetate (CAS # 68901-15-5) provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data provided allyl cyclohexanepropionate a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; allyl cyclohexanepropionate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class II material, and the exposure to allyl cyclohexanepropionate is below the TTC (and 0.47 mg/day). The environmental endpoints were evaluated; allyl cyclohexanepropionate 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.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2013d; RIFM, 2013e)
Repeated Dose Toxicity: NOAEL = 32 mg/kg/day.	RIFM (2017)
Reproductive Toxicity: Developmental toxicity and Fertility: 75 mg/kg/day.	RIFM (2011)
Skin Sensitization: NESIL = 1100 μg/cm^2.	RIFM (2015a)
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: 84% (OECD 302C)	RIFM (1998)
Bioaccumulation: Screening-level: 413.8 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 28-day Fish NOEC: 0.059 mg/L	RIFM (2020c)
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: 28-day Fish NOEC: 0.059 mg/L	RIFM (2020c)
RIFM PNEC is: 1.18 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1	

1. Identification

1. **Chemical Name:** Allyl cyclohexanepropionate
2. **CAS Registry Number:** 2705-87-5
3. **Synonyms:** Allyl cyclohexylpropionate; Allyl β-cyclohexylpropionate; Allyl 3-cyclohexylpropionate; Allyl hexahydrophenylpropionate; Cyclohexanepropionic acid, 2-propenyl ester; 2-Propen-1-yl cyclohexanepropionate; ｼｸﾛﾍｷｻﾝｱﾙｶﾝ酸(C = 2～3)ｱﾘﾙ; Allyl 3-cyclohexylpropanoate; Allyl cyclohexyl propionate; Allyl cyclohexanepropionate
4. **Molecular Formula:** $C_{12}H_{20}O_2$
5. **Molecular Weight:** 196.29
6. **RIFM Number:** 253
7. **Stereochemistry:** One stereocenter and 2 possible stereoisomers

2. Physical data

1. **Boiling Point:** 266.3 °C (RIFM, 2012b), 91 °C (Katz, 1955), 196 °C (Fragrance Materials Association [FMA]), 254.19 °C (EPI Suite)
2. **Flash Point:** 106 °C (Globally Harmonized System), $t_{1/2}$ (25 °C) for pH 4 = 90.5 h; $t_{1/2}$ (25 °C) for pH 7 (RIFM, 2012c), 106 °C (1013 hPa) (RIFM, 2012a), >212 °F; CC (FMA)
3. **Log K_{OW}:** Log Pow = 4.3 (RIFM, 2010b), 4.8 at 30 °C (RIFM, 1996a), 4.47 (EPI Suite)
4. **Melting Point**: 17.28 °C (EPI Suite)
5. **Water Solubility:** 0.017 g/L (RIFM, 2010a)
6. **Specific Gravity:** 0.945–0.950 (FMA), 0.947–0.952 (FMA)
7. **Vapor Pressure:** 3.8 Pa at 25 °C (RIFM, 2012d), 0.0137 mm Hg at 20 °C (EPI Suite v4.0), 0.01 mm Hg at 20 °C (FMA), 0.0218 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless, slightly oily liquid with a sweet, fruity, natural pineapple odor; a sweet pineapple-like taste

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.045% (RIFM, 2015b)
2. **Inhalation Exposure*:** 0.00047 mg/kg/day or 0.034 mg/day (RIFM, 2015b)
3. **Total Systemic Exposure**:** 0.0030 mg/kg/day (RIFM, 2015b)

*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 II, Intermediate

Expert Judgment	Toxtree v 3.1	OECD QSAR Toolbox v 3.2
II	II	II

2. Analogs Selected:
a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** Allyl (cyclohexyloxy)acetate (CAS # 68901-15-5)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

Allyl cyclohexanepropionate 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 02/28/20 (ECHA, 2013).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for allyl cyclohexanepropionate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.085
2	Products applied to the axillae	0.025
3	Products applied to the face/body using fingertips	0.35
4	Products related to fine fragrances	0.47
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.12
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.12
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.12
5D	Baby cream, oil, talc	0.040
6	Products with oral and lip exposure	0.28
7	Products applied to the hair with some hand contact	0.70
8	Products with significant ano-genital exposure (tampon)	0.040
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.92
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.70
10B	Aerosol air freshener	3.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.040
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

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 allyl cyclohexanepropionate, the basis was the reference dose of 0.32 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 1100 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).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, allyl cyclohexanepropionate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Allyl cyclohexanepropionate was assessed in

the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

Allyl cyclohexanepropionate was evaluated in an Ames test using strains TA98, TA100, TA1535, TA1537, and TA1538 and found to be negative (Wild, 1983). Considering the restrictions of the previous Ames test, a mammalian cell gene mutation assay (HPRT assay) was conducted according to OECD TG 476/GLP guidelines. Chinese hamster lung cells were treated with allyl cyclohexanepropionate in dimethyl sulfoxide (DMSO) at concentrations up to 2000 μg/mL (as determined in a preliminary toxicity assay) for 4 and 24 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (RIFM, 2013d). Under the conditions of the study, allyl cyclohexanepropionate was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of allyl cyclohexanepropionate 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 allyl cyclohexanepropionate in DMSO at concentrations up to 1963.0 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1963.0 μg/mL in the presence and absence of metabolic activation. Allyl cyclohexanepropionate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels or the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2013e). Under the conditions of the study, allyl cyclohexanepropionate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, allyl cyclohexanepropionate does not present a concern for genotoxic potential.

Additional References: ECHA, 2013.

Literature Search and Risk Assessment Completed On: 05/22/20.

11.1.2. Repeated dose toxicity

The MOE for allyl cyclohexanepropionate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on allyl cyclohexanepropionate. In a single-dose chronic toxicity study, groups of 5 weanling Osborne-Mendel rats/sex/dose were administered allyl cyclohexanepropionate via diet at concentrations of 0 or 2500 ppm (equivalent to 0 or 125 mg/kg/day) for 1 year. Since this is a single-dose study, it is considered inadequate to determine an accurate NOAEL for repeated dose toxicity (Hagan, 1967). In another OECD 415-compliant 1-generation study, groups of 8 Crl:CD(SD) rats/sex/dose were administered allyl cyclohexanepropionate via gavage at doses of 0, 75, 125, 250, or 500 mg/kg/day in corn oil (vehicle). However, critical parameters like hematology, clinical chemistry, urinalysis, and non-reproductive organ weights were not monitored in this study (RIFM, 2011). Hence, the study is considered insufficient for the derivation of a NOAEL for repeated dose toxicity.

Read-across material allyl (cyclohexyloxy)acetate (CAS # 68901-15-5; see Section VI) has sufficient repeated dose toxicity data for evaluation. In an OECD 407-compliant subchronic study, 5 Sprague Dawley. (Crl:CD[SD]) rats/sex/dose were administered allyl (cyclohexyloxy) acetate via gavage at concentrations of 0%, 0.01%, 0.03%, and 0.1% (equivalent to 11.5, 32.8, and 108.6 mg/kg/day for males, and 10.7, 32.2, and 96.0 mg/kg/day for females according to the study report calculations). An additional 5 (Crl:CD[SD]) rats/sex/dose at 0 and 0.1% were maintained for 14 days after the treatment period as recovery groups. No mortality occurred throughout the study period. No treatment-related effects were reported in body weight, clinical signs, functional observations, urinalysis, hematology, clinical chemistry, histopathology, estrous cycle, examination of sperm, organ weights, or necropsy. **Based on no effects seen up to the highest dose, the NOAEL was considered to be 0.1% (equivalent to 96 mg/kg/day) (RIFM, 2017).**

A default safety factor of 3 was used when deriving a NOAEL from an OECD 407 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 96/3, or 32 mg/kg/day.

Therefore, the allyl cyclohexanepropionate MOE for the repeated dose toxicity endpoint can be calculated by dividing the allyl (cyclohexyloxy)acetate NOAEL in mg/kg/day by the total systemic exposure to allyl cyclohexanepropionate, 32/0.003, or 10667.

In addition, the total systemic exposure to allyl cyclohexanepropionate (3 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Derivation of reference dose (RfD):

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) and a reference dose of 0.32 mg/kg/day.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for allyl cyclohexanepropionate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 32 mg/kg/day by the uncertainty factor, 100 = 0.32 mg/kg/day.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/22/20.

11.1.3. Reproductive toxicity

The MOE for allyl cyclohexanepropionate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. A reproduction DRF study (equivalent to OECD 421-compliant, with the exception of the number of animals) was conducted in male and female Crl:CD(SD) rats (DRF for 1-generation reproduction toxicity). Groups of 8 rats/sex/dose were gavaged daily with 0, 75, 125, 250, or 500 mg/kg/day allyl cyclohexanepropionate in corn oil (vehicle). Allyl cyclohexanepropionate increased the incidence of mortality in P generation male and female rats given 250 or 500 mg/kg/day. Reproductive organ weights were unaffected by oral administration of allyl cyclohexanepropionate. The average pup body weight on postpartum day 1 was reduced by 12% at 125 mg/kg/day; however, these reductions were transient and had resolved by postpartum day 5. The NOAEL for developmental toxicity and fertility was determined to be 75 mg/kg/day, based on transient reductions in pup body weights and mortality observed in P generation rats (RIFM, 2011). These effects were observed at maternally toxic dosages. Only a dose range finding (DRF) study was conducted on allyl cyclohexanepropionate, which was not considered sufficient.

Therefore, the allyl cyclohexanepropionate MOE for the developmental toxicity and fertility endpoint can be calculated by dividing the allyl cyclohexanepropionate NOAEL in mg/kg/day by the total systemic exposure to allyl cyclohexanepropionate, 75/0.003 or 25000.

In addition, the total systemic exposure to allyl cyclohexanepropionate (3 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007; Laufersweiler, 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: 05/20/20.

11.1.4. Skin sensitization

Based on the existing data, allyl cyclohexanepropionate is considered a skin sensitizer with a defined NESIL of 1100 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, allyl cyclohexanepropionate is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2; TIMES-SS v2.28.16). In a guinea pig maximization test, allyl cyclohexanepropionate led to skin sensitization reactions at 100% (ECHA, 2013). In a Draize test, 0.025% solution of allyl cyclohexanepropionate did not induce sensitization reactions in any of the guinea pigs (RIFM, 1970). In 2 human maximization tests, no skin sensitization reactions were observed at 4% or 2760 μg/cm^2 of allyl cyclohexanepropionate (RIFM, 1974; RIFM, 1971). Additionally, in a Confirmation of No Induction in Humans (CNIH) test with 1% or 1181 μg/cm^2 of allyl cyclohexanepropionate in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 106 volunteers (RIFM, 2015a).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, allyl cyclohexanepropionate is a weak sensitizer with a WoE NESIL of 1100 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) and a reference dose of 0.32 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/08/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, allyl cyclohexanepropionate 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 allyl cyclohexanepropionate 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, 2009). Based on the lack of absorbance, allyl cyclohexanepropionate does not present a concern for phototoxicity or photoallergenicity.

Table 1
Data summary for allyl cyclohexanepropionate.

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
NA	Weak	1181	2760	NA	1100

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; 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 test or HMT.

[c] WoE NESIL limited to 2 significant figures.

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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/08/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for allyl cyclohexanepropionate is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on allyl cyclohexanepropionate. Based on the Creme RIFM Model, the inhalation exposure is 0.034 mg/day. This exposure is 13.82 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/04/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of allyl cyclohexanepropionate 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, allyl cyclohexanepropionate 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 v4.1 (US EPA, 2012a) did not identify allyl cyclohexanepropionate as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on current VoU (2015), allyl cyclohexanepropionate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. ***Biodegradation:***

RIFM, 2008: A modified biodegradation study according to the OECD 310 method was conducted. After 56 days, biodegradation of 71% was observed.

RIFM, 1996b: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. The test material underwent 56% biodegradation after 28 days in the test conditions.

RIFM, 1998: Inherent biodegradability of the test material was determined by the manometric respirometry test according to the OECD 302C method. Biodegradation of 84% was observed after 28 days.

Ecotoxicity:

RIFM, 2013b: A 96-h fathead minnow (*Pimephales promelas*) acute test was conducted according to the OECD 203 guidelines under flow-through conditions. The 96-h LC50 was 0.13 mg/L.

RIFM, 2013c: A 96-h algae acute test was conducted according to the OECD 201 guidelines. The test was conducted using a closed-bottle test designed with pre-conditioned glassware in an attempt to improve analytical recoveries. The 72-h EbC50 was 2.1 mg/L (area under the growth curve) and ErC50: 3.0 mg/L (growth rate). Values were calculated, when possible, using non-linear regression with replicate data and day 0 measured test concentrations.

RIFM, 2013a: A 48-h *Daphnia magna* acute test was conducted according to the OECD 202 guidelines under flow-through conditions. The EC50 was reported to be 3.8 mg/L.

RIFM, 2020c: An early life-stage toxicity test with fathead minnow was conducted according to the OECD 210 guidelines under flow-through conditions. Based on mean measured concentrations, the 28-day NOEC was reported to be 0.059 mg/L based on survival and growth. The 28-day EC10, based on post-hatch larval survival, was reported to be 0.064 mg/L.

Other available data:

Allyl cyclohexanepropionate has been registered under REACH and a full dossier is available. However, no additional data for allyl cyclohexanepropionate is available.

11.2.3. 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, 2002).

Exposure	Europe	North America
Log K_{ow} Used	4.8	4.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
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 1.18 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, allyl cyclohexanepropionate does not present a risk to

RIFM Framework Screening-level **(Tier 1)**	0.970			1000000	0.00097	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.946	1.510	0.435			Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.553	1.872	<u>0.407</u>	10000	0.0407	Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.974	0.695	1.329			Neutral organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.13		<u>0.059</u>	50	1.18	
Daphnia		3.8				
Algae		0.74	0.28			

the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 02/05/20.

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 04/21/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112424.

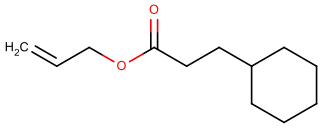
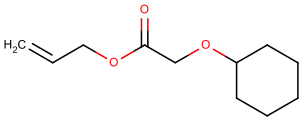
Appendix B

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with 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 material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Allyl cyclohexanepropionate	Allyl (cyclohexyloxy)acetate
CAS No.	2705-87-5	68901-15-5
Structure		
Similarity (Tanimoto Score)		0.48
		• Repeated dose toxicity
Molecular Formula	$C_{12}H_{20}O_2$	$C_{11}H_{18}O_3$

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Molecular Weight	196.29	198.26
Melting Point (°C, EPI Suite)	17.28	22.95
Boiling Point (°C, EPI Suite)	254.19	254.86
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.91	2.80
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	17*	211.10
Log K_{OW}	4.47	2.72
J_{max} (μg/cm^2/h, SAM)	0.95	4.38
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	74.78	3.52
Repeated Dose Toxicity		
Repeated Dose (HESS)	Allyl esters (Hepatotoxicity) Rank A	Allyl esters (Hepatotoxicity) Rank A
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

*(RIFM, 2010a).

Summary

There are insufficient toxicity data on allyl cyclohexanepropionate (CAS # 2705-87-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, allyl (cyclohexyloxy)acetate (CAS # 68901-15-5) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Allyl (cyclohexyloxy)acetate (CAS # 68901-15-5) was used as a read-across analog for the target material allyl cyclohexanepropionate (CAS # 2705-87-5) for the repeated dose toxicity endpoint.

o The target material and the read-across analog are structurally similar and belong to the structural class of allyl esters.
oThe key difference between the target material and the read-across analogs that the target is a 3-carbon ester whereas the read-across is a 2-carbon ester. Moreover, the target has a cyclohexane ring whereas the read-across analog has a cyclohexyloxy ring which introduces an ether linkage. This structural difference is toxicologically insignificant.
oThe similarity between the target material and the read-across analog is indicated by the Tanimoto score presented in the table above. The differences in the structures which are responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.
oThe physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
oAccording to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
oThe target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
oThe structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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