Food and Chemical Toxicology 182 (2023) 114254

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, allyl cyclohexaneacetate, CAS Registry Number 4728-82-9

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], M. Date [a], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], M. Na [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. Dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

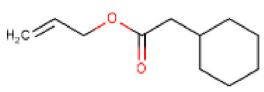
ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2023.114254
Received 29 September 2022; Received in revised form 25 September 2023; Accepted 21 November 2023
Available online 28 November 2023

Version: 092722. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: Allyl cyclohexaneacetate CAS Registry Number: 4728-82-9

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., 2021)
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; Safford et al., 2017) compared to a deterministic aggregate approach
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 et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Allyl cyclohexaneacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog allyl cyclohexanepropionate (CAS # 2705-87-5) show that allyl cyclohexaneacetate is not expected to be genotoxic and provided a calculated Margin of Exposure (MOE) > 100 for the reproductive toxicity endpoint and a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm^2 for the skin sensitization endpoint. Data on read-across analog allyl (cyclohexyloxy)acetate (CAS # 68901-15-5) provide a calculated MOE >100 for the repeated dose toxicity endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; allyl cyclohexaneacetate is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to allyl cyclohexaneacetate is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; for the hazard assessment based on the screening data, allyl cyclohexaneacetate is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, allyl cyclohexaneacetate was not able to be risk screened as there were no reported volumes of use (VoU) for either North America or Europe in the 2019 IFRA Survey.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2013a; RIFM, 2013b)
Repeated Dose Toxicity: NOAEL = 32 mg/kg/day.	RIFM (2017)
Reproductive Toxicity: Developmental toxicity and Fertility NOAEL: 75 mg/kg/day.	RIFM (2011)
Skin Sensitization: NESIL = 1100 μg/cm^2.	RIFM (2015)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

(*continued on next page*)

(*continued*)

Persistence:	
Screening-level: 2.94 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 196.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Not applicable	
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:
- Not applicable; no VoU in 2019 reported for Europe and North America

1. Identification

1. **Chemical Name:** Allyl cyclohexaneacetate
2. **CAS Registry Number:** 4728-82-9
3. **Synonyms:** Allyl cyclohexylacetate; Allyl hexahydrophenylacetate; Cyclohexaneacetic acid, 2-propenyl ester; 2-Propen-1-yl cyclohexaneacetate; Allyl cyclohexaneacetate
4. **Molecular Formula:** $C_{11}H_{18}O_2$
5. **Molecular Weight:** 182.26 g/mol
6. **RIFM Number:** 567
7. **Stereochemistry:** One stereocenter and 2 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 66 °C (Katz, 1955), 236.46 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.98 (EPI Suite)
4. **Melting Point**: 6.46 °C (EPI Suite)
5. **Water Solubility:** 21.44 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0359 mm Hg at 20 °C (EPI Suite v4.0), 0.0558 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with mixed fruity, sweet, lasting odor. The flavor is overall fruity.

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00015% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.00020 mg/kg/day or 0.013 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00023 mg/kg/day (RIFM, 2018)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford, 2015; Safford, 2017; 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, 2015; Safford, 2017; Comiskey et al., 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 v3.1	OECD QSAR Toolbox v4.2
II	II	II

2. **Analogs Selected:**
   a. **Genotoxicity:** Allyl cyclohexanepropionate (CAS # 2705-87-5)
   b. **Repeated Dose Toxicity:** Allyl (cyclohexyloxy)acetate (CAS # 68901-15-5)
   c. **Reproductive Toxicity:** allyl cyclohexanepropionate (CAS # 2705-87-5)
   d. **Skin Sensitization:** Allyl cyclohexanepropionate (CAS # 2705-87-5)
   e. **Photoirritation/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 cyclohexaneacetate 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

Allyl cyclohexaneacetate has been pre-registered for 2010; no dossier available as of 09/12/22.

10. Conclusion

The maximum acceptable concentrations in finished products for

allyl cyclohexaneacetate 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)	0.070
2	Products applied to the axillae	0.025
3	Products applied to the face/body using fingertips	0.070
4	Products related to fine fragrances	0.070
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.070
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.070
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.070
5D	Baby cream, oil, talc	0.023
6	Products with oral and lip exposure	0.070
7	Products applied to the hair with some hand contact	0.070
8	Products with significant ano-genital exposure (tampon)	0.023
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)	0.77
10B	Aerosol air freshener	0.35
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.023
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 cyclohexaneacetate, 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; December 2019).

[c] Calculations by Creme RIFM Aggregate Exposure Model v3.2.6.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Allyl cyclohexaneacetate 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.

There are no studies assessing the mutagenic or clastogenic activity of allyl cyclohexaneacetate; however, read-across can be made to allyl cyclohexanepropionate (CAS # 2705-87-5; see Section VI).

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, 2013a). Under the conditions of the study, allyl cyclohexanepropionate was not mutagenic to mammalian cells *in vitro*, and this can be extended to allyl cyclohexaneacetate.

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 the 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, 2013b). Under the conditions of the study, allyl cyclohexanepropionate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to allyl cyclohexaneacetate.

Based on the data available, allyl cyclohexanepropionate does not present a concern for genotoxic potential, and this can be extended to allyl cyclohexaneacetate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on allyl cyclohexaneacetate. Read-across material allyl (cyclohexyloxy)acetate (CAS # 68901-15-5; see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

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) for 28 days. 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 cyclohexaneacetate 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 cyclohexaneacetate, 32/0.00023, or 139130.

In addition, the total systemic exposure to allyl cyclohexaneacetate (0.23 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

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. (2020) and a subchronic reference dose (RfD) of 0.32 mg/kg/day.

11.1.3. Derivation of subchronic RfD

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for inter-species (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for allyl cyclohexaneacetate was calculated by dividing the lowest NOAEL (from the Repeated Dose or 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: 06/21/21.

11.1.4. Reproductive toxicity

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

11.1.4.1. Risk assessment. There are no reproductive toxicity data on allyl cyclohexaneacetate. Read-across material allyl cyclohexanepropionate (CAS # 2705-87-5; see Section VI) has sufficient data to support the reproductive toxicity endpoint.

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). Parental (P) generation male rats were given the test material and/or the vehicle once daily beginning at least 14 days before cohabitation, through cohabitation (maximum duration of 7 days), and continuing through the day before scheduled euthanasia. P generation female rats were given the test material and/or the vehicle once daily beginning at least 14 days before cohabitation, through cohabitation (maximum duration of 7 days), and continuing through day 25 of presumed gestation (rats that did not deliver) or day 4 postpartum (rats that delivered a litter). Pups (F1 generation litters) were not administered the test material directly but may have been exposed in utero during gestation or via maternal milk and maternal feed during the postpartum period. Male rats were euthanized after the completion of the cohabitation period. Female rats were allowed to deliver their litters and were euthanized on day 5 postpartum. F1 generation pups were euthanized on day 5 postpartum. Allyl cyclohexanepropionate increased the incidence of mortality in P-generation male and female rats that were 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.

Therefore, the allyl cyclohexaneacetate MOE for the developmental toxicity and fertility endpoints can be calculated by dividing the allyl cyclohexanepropionate NOAEL in mg/kg/day by the total systemic exposure to allyl cyclohexaneacetate, 75/0.00023 or 326087.

In addition, the total systemic exposure to allyl cyclohexaneacetate (0.23 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/21/21.

11.1.5. Skin sensitization

Based on the existing data and read-across allyl cyclohexanepropionate (CAS # 2705-87-5), allyl cyclohexaneacetate is considered a skin sensitizer with a defined NESIL of 1100 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

11.1.5.1. Risk assessment. Insufficient skin sensitization studies are available for allyl cyclohexaneacetate. Based on the existing data and read-across material allyl cyclohexanepropionate (CAS # 2705-87-5; see Section VI), allyl cyclohexaneacetate is considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, read-across material allyl cyclohexanepropionate led to skin sensitization reactions at 100% (ECHA, 2013; RIFM, 2012). In a guinea pig Draize test, 0.025% solution of read-across material allyl cyclohexanepropionate in 0.9% saline did not induce sensitization reactions (RIFM, 1970). In a human maximization test with allyl cyclohexaneacetate and 2 additional human maximization tests with read-across material allyl cyclohexanepropionate, no skin sensitization reactions were observed at 4% or 2760 μg/cm^2 of (RIFM, 1974a; RIFM, 1974c; RIFM, 1971). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 1% or 1181 μg/cm^2 of read-across material allyl cyclohexanepropionate in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 106 volunteers (RIFM, 2015).

Based on weight of evidence (WoE) from structural analysis, human study data, and data on the read-across material allyl cyclohexanepropionate, allyl cyclohexaneacetate is a sensitizer with a WoE NESIL of 1100 μg/cm^2 (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. (2020) and a subchronic RfD of 0.32 mg/kg/day.

Additional References: RIFM, 1974b; NICNAS, 2019; NICNAS, 2018; RIFM, 1998.

Literature Search and Risk Assessment Completed On: 09/27/22.

11.1.6. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, allyl cyclohexaneacetate would not be expected to present a concern for photoirritation or photoallergenicity.

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

11.1.6.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/26/21.

Table 1
Data summary for allyl cyclohexanepropionate as read-across material for allyl cyclohexaneacetate.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL[2] (induction) µg/cm²	WoE NESIL[3] µg/cm²	LLNA Weighted Mean EC3 Value µg/cm²	GPMT[4]	Buehler[4]
Weak	1181	2760	NA	1100	NA	Positive	NA
	In vitro Data[5]				*In silico* protein binding alerts (OECD Toolbox v4.2)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	NA	NA	NA		SN2	SN2	SN2

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.
[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
[2]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Studies conducted according to the OECD TG 406 are included in the table.
[5]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

11.1.7. Local respiratory toxicity

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

11.1.7.1. Risk assessment. There are no inhalation data available on allyl cyclohexaneacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.013 mg/day. This exposure is 36.2 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/19/21.

11.2. 2. environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of allyl cyclohexaneacetate 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. 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 cyclohexaneacetate was not able to be risk screened as there were no reported VoU for either North America or Europe in the 2019 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify allyl cyclohexaneacetate 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, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model

outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bio-accumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Not applicable. No VoU in 2019 reported for Europe and North America.

11.2.1.2. Key studies. Biodegradation:
No data available.
Ecotoxicity:
No data available.

11.2.1.3. Other available data. Allyl cyclohexaneacetate has been pre-registered for REACH, with no additional information available at this time.

Risk Assessment Refinement: Not applicable.

Literature Search and Risk Assessment Completed On: 09/09/22.

*11.3. 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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/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 09/27/22.

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.2023.114254.

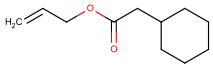
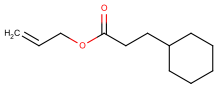
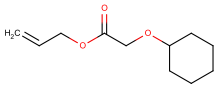
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). 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, 2017b).

- 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	Read-across Material
Principal Name	Allyl cyclohexaneacetate	Allyl cyclohexanepropionate	Allyl (cyclohexyloxy)acetate
CAS No.	4728-82-9	2705-87-5	68901-15-5
Structure			
Similarity (Tanimoto Score)		0.70	0.60
Endpoint		• Genotoxicity • Skin sensitization • Reproductive toxicity	• Repeated dose toxicity
Molecular Formula	$C_{11}H_{18}O_2$	$C_{12}H_{20}O_2$	$C_{11}H_{18}O_3$
Molecular Weight (g/mol)	182.26	196.29	198.26
Melting Point (°C, EPI Suite)	6.46	17.28	22.95
Boiling Point (°C, EPI Suite)	236.46	254.19	254.86
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.44	2.91	2.80
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	21.44	6.95	211.10
Log K_{OW}	3.98	4.47	2.72
J_{max} (μg/cm^2/h, SAM)	2.60	0.95	4.38
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	56.34	74.78	3.52
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	
Carcinogenicity (ISS)	No alert found	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	
Oncologic Classification	Not classified	Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Allyl esters (Hepatotoxicity) Rank A		Allyl esters (Hepatotoxicity) Rank A
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group	Non-binder, without OH or NH2 group	
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (moderate reliability)	Non-toxicant (moderate reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters	
Protein Binding (OECD)	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals	
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)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Acyl Transfer agent identified.	Alert for Acyl Transfer agent 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	See Supplemental Data 3

Summary

There are insufficient toxicity data on allyl cyclohexaneacetate (CAS # 4728-82-9). Hence, *in silico* evaluation was conducted to determine read-across material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, allyl cyclohexanepropionate (CAS # 2705-87-5) and allyl (cyclohexyloxy)acetate (CAS # 68901-15-5) were identified as read-across materials with sufficient toxicological data for their respective toxicity endpoints.

Conclusions

- Allyl cyclohexanepropionate (CAS # 2705-87-5) was used as a read-across analog for the target material allyl cyclohexaneacetate (CAS # 4728-82-9) for the genotoxicity, skin sensitization, and reproductive toxicity endpoints.

- The target material and the read-across analog belong to the generic class of aliphatic esters in which the acid portion is an extended fragment on a cyclohexane ring.
- The key difference between the target material and the read-across analog is that the target material is an acetate, while the read-across analog is a propionate. This structural difference is toxicologically insignificant.
- Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the ethyl benzene fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog have several protein-binding alerts. Data described in the skin sensitization section above are consistent with *in silico* alerts and show that the read-across analog does not pose a concern for skin sensitization.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Allyl (cyclohexyloxy)acetate (CAS # 68901-15-5) was used as a read-across analog for the target material allyl cyclohexaneacetate (CAS # 4728-82-9) for the repeated dose toxicity endpoint.
  - The target material and the read-across analog belong to the generic class of aliphatic esters.
  - The key difference between the target material and the read-across analog is that the target material has a cyclohexyl substituent on the acid side while the read-across analog has a cyclohexyloxy substituent. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the ethyl benzene fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog have several protein-binding alerts. Data described in the skin sensitization section above are consistent with *in silico* alerts and show that the read-across analog does not pose a concern for skin sensitization.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

Api, A.M., Basketter, D., Bridges, J., Cadby, P., et al., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 2020 (118), 104805.

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

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

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

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

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

Cottrez, F., Boitel, E., Ourlin, J.C., Peiffer, J.L., et al., 2016. A 3D reconstituted epidermis based model for quantifying chemical sensitization potency: reproducibility and predictivity results from an inter-laboratory study. Toxicol. Vitro 32, 248–260. Apr.

Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718, 2020.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.8: Characterisation of Dose [concentration]-Response for Human Health. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2013. Allyl 3-cyclohexylpropionate Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/12564/1/2.

ECHA, 2017a. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017b. Read-across Assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

Forreryd, A., Zeller, K.S., Lindberg, T., Johansson, H., Linstedt, M., 2016. From genome-wide arrays to tailor-made biomarker readout - progress towards routine analysis of skin sensitizing chemicals with GARD. Toxicol. Vitro 37, 178–188.

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

IFRA (International Fragrance Association), 2019. Volume of Use Survey, January-December 2019.

Katz, A., 1955. Highlights on newly developed flavoring aromatics. Food Technol. 9 (12), 636–638.

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

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

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

NICNAS, 2018. Aliphatic Allyl Esters: Human Health Tier II Assessment. Retrieved from. https://www.industrialchemicals.gov.au/sites/default/files/Aliphatic%20allyl%20esters_Human%20health%20tier%20II%20assessment.pdf.

NICNAS, 2019. Allyl Esters of Acetic Acid Ethers: Human Health Tier II Assessment. Retrieved from. https://www.industrialchemicals.gov.au/sites/default/files/Allyl%20esters%20of%20acetic%20acid%20ethers_Human%20health%20tier%20II%20assessment.pdf.

OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA)*. ENV/JM/HA(2015), p. 7. Retrieved from. https://one.oecd.org/document/ENV/JM/HA(2015)7/en/pdf.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1970. Sensitization Test with Allyl Cyclohexanepropionate in guinea Pigs. Unpublished Report from IFF Incorporated. RIFM Report Number 47360. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1971. Appraisal of Sensitizing Powers by Maximization Testing in Humans. Report to RIFM. RIFM Report Number 1805. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1974a. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1801. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1974b. Acute Toxicity Studies with Allyl (Cyclohexyloxy)acetate (Cyclogalbanat). Unpublished Report from Symrise. RIFM Report Number 58167. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1974c. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1799. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1998. Repeated Application Closed Patch Epicutaneous Test of Allyl (Cyclohexyloxy)acetate (Isoananat) under Occlusion. Unpublished Report from Haarmann & Reimer GmbH. RIFM Report Number 35033. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2011. Oral (Gavage) Dosage-Range Reproduction Study of Allyl Cyclohexanepropionate in Rats. RIFM Report Number 61820. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012. Allyl Cyclohexanepropionate: Guinea Pig Sensitization Maximization Test. Unpublished Report from Symrise. RIFM Report Number 67897. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. Gene Mutation Assay in Chinese Hamster V79 Cells in Vitro (V79/HPRT) with Allyl Cyclohexanepropionate (Allyl Cyclo Hexyl Propionate). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 65218.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Allyl Cyclohexanepropionate: in Vitro Micronucleus Test in Human Lymphocytes. Unpublished Report from Symrise. RIFM Report Number 67893. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Report on the Testing of Allyl Cyclohexaneacetate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 67564. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015. Allyl Cyclohexanepropionate: Repeated Insult Patch Test (RIPT). RIFM Report Number 68424. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Allyl (Cyclohexyloxy) acetate (Cyclogalbanat): 4-Week Repeated Oral (Dietary) Dose Toxicity Study with a Two-Week Recovery Period in Sprague-Dawley Rats. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 72795.
RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Exposure Survey 21. September 2018.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.