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RIFM fragrance ingredient safety assessment, allyl (cyclohexyloxy)acetate, CAS registry number 68901-15-5

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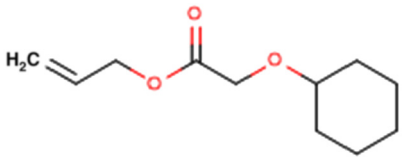

Abbreviation/Definition list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5 percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF – Assessment Factor
DEREK – Derek nexus is an *in silico* tool to predict whether a chemical will be toxic
DST – Dermal Sensitization Threshold
ECHA – European Chemicals Agency
GLP – Good Laboratory Practice

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0278-6915/

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
NESIL – No Expected Sensitization Induction Level
NOAEC – No Observed Adverse Effect Concentration
NOAEL – No Observed Adverse Effect Level
NOEC – No Observed Effect Concentration
OECD – Organisation for Economic Co-operation and Development
OECD TG – Organisation for Economic Co-operation and Development Testing Guidelines
PBT – Persistent, Bioaccumulative, and Toxic
PEC/PNEC – Predicted Environmental Concentration/Predicted No Effect Concentration
QRA – quantitative risk assessment
REACH – Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM – Research Institute for Fragrance Materials
RQ – Risk Quotient
TTC – Threshold of Toxicological Concern
UV/Vis Spectra – Ultra Violet/Visible spectra
VCF – Volatile Compounds in Food
VoU – Volume of Use
vPvB – (very) Persistent, (very) Bioaccumulative

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on RIFM's Criteria Document (Api et al., 2015) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria such as, acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
* RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for Genotoxicity, Repeated Dose Toxicity, Developmental Toxicity, Reproductive Toxicity, Local Respiratory Toxicity, Phototoxicity, Skin Sensitization potential as well as Environmental assessment. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 7.5 mg/kg/day, based on a gavage reproduction dosage-range finding study conducted in rats on a read across analog, that resulted in a MOE of 441 considering 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 1999a; Wild et al., 1983)
Repeated Dose Toxicity: NOAEL = 7.5 mg/kg/day (RIFM, 2011)
Developmental and Reproductive Toxicity: NOAEL = 75 mg/kg/day (RIFM, 2011)
Skin Sensitization: Not a Sensitization Concern (RIFM, 1974, 1978, 1989a, 1999b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM Database)
Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 24.1% (BOD) (RIFM, 1995b)
Bioaccumulation: Screening Level: 29.1 L/kg (EPISUITE ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint**:** Fish 96 hr LC50: 1.101 mg/L (ECOSAR ver 1.11)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-Level: PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish 96 hr LC50: 1.101 mg/L (ECOSAR ver 1.11)
RIFM PNEC is: 0.1101 μg/L
• Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** Allyl (cyclohexyloxy)acetate
2. **CAS Registry Number:** 68901-15-5
3. **Synonyms:** Acetic acid, (cyclohexyloxy)-, 2-propenyl ester, Allyl (cyclohexyloxy)acetate, Cyclogalbanate, Cyclogalbaniff, Isoananat, Cyclogalbanat, 2-シクロヘキシルオキシ酢酸=プロパ-2-エン-1-イル
4. **Molecular Formula:** $C_{11}H_{18}O_3$
5. **Molecular Weight:** 198.62
6. **RIFM Number:** 5937

2. Physical data

1. **Boiling Point:** 254.86 °C [EPI Suite]
2. **Flash Point:** > 212.00 °F TCC (>100.00 °C)*
3. **Log K_{ow}:** 2.72 [EPI Suite]
4. **Melting Point**: 22.95 °C [EPI Suite]
5. **Water Solubility:** 211.1 mg/L [EPI Suite]
6. **Specific Gravity:** 1.01200 to 1.02000 @ 25.00 °C*
7. **Vapor Pressure:** 0.021 mm Hg @ 25 °C [EPI Suite], 0.0132 mm Hg @ 20 °C [EPI Suite 4.0]
8. **UV Spectra:** Does not significantly absorb in the region of 290–700 nm; molar absorption coefficient is below the benchmark.
9. **Appearance/Organoleptic:** Colorless clear liquid with a medium green, galbanum, fruity, and pineapple odor when smelled in a 10.00% solution or less (Luebke, William tgsc, 1992)*

* http://www.thegoodscentscompany.com/data/rw1038701.html, retrieved 03/05/14.

3. Exposure

1. **Volume of Use (worldwide band):** 10 to 100 metric tons per year (IFRA, 2011)

2. **Average Maximum Concentration in Hydroalcoholics:** 0.36% (IFRA, 2008)
3. **97.5th Percentile:** 0.64% (IFRA, 2008)
4. **Dermal Exposure*:** 0.0163 mg/kg/day (IFRA, 2008)
5. **Oral Exposure:** Not available
6. **Inhalation Exposures**:** 0.00099 mg/kg/day (IFRA, 2008)
7. **Total Systemic Exposure (Dermal + Inhalation):** 0.017 mg/kg/day

* Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., antiperspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

** Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Data not available – not considered.
3. **Inhalation:** Assumed 100%
4. **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.017 mg/kg/day

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High

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

2. **Analogs Selected:**
   a. **Genotoxicity:** Allyl cyclohexanepropionate (CAS # 2705-87-5)
   b. **Repeated Dose Toxicity:** Allyl cyclohexanepropionate (CAS # 2705-87-5)
   c. **Developmental and Reproductive Toxicity:** Allyl cyclohexanepropionate (CAS # 2705-87-5)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justifications: See Appendix below**

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

Allyl (cyclohexyloxy)acetate is not reported to occur in food by the VCF.*

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

7. IFRA standard

IFRA Standard Specification. Use only when the level of free allyl alcohol is less than 0.1%. Based on the delayed irritant potential of allyl alcohol (FCT 15, 611, 1977).

8. REACH dossier

Pre-Registered for 2010; No dossier available as of 01/22/15.

9. Summary

9.1. Human health endpoint summaries

9.1.1. Genotoxicity

Based on the current existing data and use levels, allyl (cyclohexyloxy)acetate does not present a concern for genetic toxicity.

9.1.1.1. Risk assessment. The mutagenic activity of allyl (cyclohexyloxy)acetate was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA 1535, TA 1537, TA 102, TA 98 and TA 100 were treated with allyl (cyclohexyloxy)acetate at concentrations up to 5000 µg/plate in the presence and absence of metabolic activation. No increase in the number of revertant colonies was detected in the strains at the concentrations tested (RIFM, 1999a). Under the conditions of the study, allyl (cyclohexyloxy)acetate was considered not mutagenic.

There are no data assessing the clastogenic potential of allyl (cyclohexyloxy)acetate. The material allyl cyclohexane propionate (CAS # 2705-87-5; see Section 5) was identified as a read across analog whose clastogenic potential was assessed in an *in vivo* micronucleus test in which groups of male and female NMRI mice were dosed once at 3–4 dose levels up to a maximum of 1540 mg/kg b.w. of 2,6-dimethyl-5-heptenal in olive oil (Wild et al., 1983). Under the conditions of the study, the analog was considered non-clastogenic and this can be extended to allyl (cyclohexyloxy)acetate.

Based on all the data available, allyl (cyclohexyloxy) acetate does not present a concern for genotoxic potential.

Additional References: RIFM (2013).

Literature Search and Risk Assessment Completed on: 02/09/14.

9.1.2. Repeated dose toxicity

The margin of exposure for allyl (cyclohexyloxy)acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

9.1.2.1. Risk assessment. There are no repeated dose toxicity data on allyl (cyclohexyloxy)acetate. Read across material allyl cyclohexanepropionate (CAS # 2705-87-5; see Section 5) has a gavage reproduction dosage-range finding study conducted in rats (RIFM, 2011). The LOAEL for general toxicity was determined to be 75 mg/kg/day, based on histopathological changes in the liver (multifocal necrosis, periportal vacuolation of hepatocytes, and colangiofibrosis). The liver changes were observed in a dose–responsive manner. The NOAEL was derived by dividing the LOAEL by a safety factor of 10, which is equal to 7.5 mg/kg/day (ECHA, 2010). Additionally, allyl cyclohexanepropionate was tested via dietary exposure to rats, an exposure route more relevant to human exposure to fragrance ingredients than gavage. No effects were observed after dietary exposures to 2500 ppm, or 125 mg/kg/day, for 1-year in a chronic toxicity study conducted in rats (Hagan et al., 1967). The most conservative NOAEL was selected for this safety assessment. **Therefore, the MOE is equal to the allyl cyclohexanepropionate NOAEL in mg/kg/day divided by the total systemic exposure, 7.5/0.017 or 441.**

Additional References: Auerbach et al., 2008; Bär et al., 1967; Berman et al., 1992; Butterworth et al., 1978; Carpanini et al., 1978; Dunlap et al., 1955; Dunlap et al., 1959; ECHA REACH Dossier: Allyl alcohol; Jenkinson et al., 1990; Lake et al., 1978; Lijinsky et al., 1987; McLaughlin et al., 1964; OECD SIDS, 2005; RIFM, 2006; Slott et al.,

1984, 1985; Smyth et al., 1951; Torkelson et al., 1959; Zava et al., 1998.

Literature Search and Risk Assessment Completed on: 02/14/14.

9.1.3. Developmental and reproductive toxicity

The margin of for allyl (cyclohexyloxy)acetate exposure is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

9.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on allyl (cyclohexyloxy)acetate. Read across material, allyl cyclohexanepropionate (CAS # 2705-87-5; see Section 5) has a gavage reproduction dosage-range finding study conducted in rats (RIFM, 2011). The NOAEL for developmental and reproductive toxicity was determined to be 75 mg/kg/day, based on transient reductions in pup body weights. These effects were observed at maternally toxic dosages. **Therefore, the MOE for developmental and reproductive toxicity is equal to the allyl cyclohexanepropionate NOAEL in mg/kg/day divided by the total systemic exposure, 75/0.017 or 4412.**

Additional References: Auerbach et al., 2008; Bär et al., 1967; Berman et al., 1992; Butterworth et al., 1978; Carpanini et al., 1978; Dunlap et al., 1955, 1959; ECHA REACH Dossier: Allyl alcohol; Jenkinson et al., 1990Lake et al., 1978; Lijinsky et al., 1987; McLaughlin et al., 1964; RIFM, 2006; OECD SIDS, 2005; Slott et al., 1984, 1985; Smyth et al., 1951; Torkelson et al., 1959; Zava et al., 1998.

Literature Search and Risk Assessment Completed on: 02/14/14.

9.1.4. Skin sensitization

Based on a weight of evidence, allyl (cyclohexyloxy)acetate does not present a concern for skin sensitization.

9.1.4.1. Risk assessment. The chemical structure of this material indicates that it has the potential to react with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In a local lymph node assay, a positive response was observed at concentrations ranging from 1% to 30%; however the irritant potential of the material suggests that the results are due to irritant responses in the assay (RIFM, 1995a). However, in a series of well conducted guinea pig tests, no reactions indicative of sensitization were observed (RIFM, 1974, 1978, 1989a, 1999b). In human repeated insult patch tests (HRIPT), no reactions considered indicative of skin sensitization were observed (RIFM, 1989b, 1989c).

Based on a weight of evidence, allyl (cyclohexyloxy)acetate does not present a concern for skin sensitization but due to its irritation potential it currently has an IFRA standard (specification) limiting the level of free allyl alcohol to less than 0.1%.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/14/14.

9.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra, allyl (cyclohexyloxy)acetate does not present a concern for phototoxicity or photoallergenicity.

9.1.5.1. Risk assessment. The available spectra for allyl (cyclohexyloxy)acetate demonstrates that this material has limited absorption in the region of 290–700 nm. However, the molar absorption coefficient for λ_{max} between 290 and 700 nm is well below the benchmark (1000 L mol^{-1} cm^{-1}) considered to be of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/14/14.

9.1.6. Local respiratory toxicity

The margin of exposure for allyl (cyclohexyloxy)acetate could not be calculated due to lack of appropriate data. Allyl (cyclohexyloxy)acetate is below the exposure level for the inhalation TTC Cramer Class III limit for local effects.

9.1.6.1. Risk assessment. There are no inhalation data available on allyl (cyclohexyloxy)acetate. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.64%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the inhalation combined exposure would be 0.059 mg/day as calculated by the RIFM 2 Box Model and further refined using Multiple Path Particle Deposition Model using the 97.5th percentile. This is below the recommended Cramer Class III TTC level of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009) and is deemed safe for use at the reported use level.

Additional References: Carpenter et al., 1949; Dunlap et al., 195, 1959; Li et al., 2012Luan et al., 2006; McCord, 1932; RIFM, 1997; Smyth et al., 1948; Torkelson et al., 1959; Zissu, 1995; Zwart et al., 1992.

Literature Search and Risk Assessment Completed on: 02/05/14.

9.2. Environmental endpoint summary

9.2.1. Screening-level assessment

A screening level risk assessment of allyl (cyclohexyloxy)acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002) that provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Following the RIFM Environmental Framework, allyl (cyclohexyloxy)acetate was identified as a fragrance material with potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify allyl (cyclohexyloxy)acetate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical–chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

9.2.2. Risk assessment

Based on current VoU (2011), allyl (cyclohexyloxy)acetate presents a risk to the aquatic compartment in the screening level assessment.

9.2.2.1. Biodegradation. The biodegradability of the test material was determined with the biological oxygen demand test for insoluble substances (BODIS). The average degradation rate of test material was 24.1% at the end of the test (28 days) (RIFM, 1995b).

A biodegradation study was conducted using activated sludge according to the C.4-E of the Annex to Directive 92/69/EEC method. Allyl (cyclohexyloxy)acetate underwent 24% degradation in 28 days (RIFM, 1996).

9.2.2.2. Ecotoxicity. A 48 hour Daphnia magna acute toxicity test was conducted following the (C.2) Directive 92/69/EEC method. The geometric mean of EC0/EC100 was reported to be 11.3 mg/L (RIFM, 1996).

Other available data: Allyl (cyclohexyloxy)acetate has been pre-registered under REACH with no additional data at this time.

9.2.3. 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.

	LC50 (Fish) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	63.33 mg/L			1,000,000	0.0633 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	10.02 mg/L	19.28 mg/L	7.321 mg/L			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.101 mg/L	7.308 mg/L	1.849 mg/L	10,000	0.1101 µg/L	Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	36.51 mg/L	22.16 mg/L	21.76 mg/L			Neutral organics SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.72	
Biodegradation Factor Used	1	
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on available data, the RQ for this material is <1. Additional assessment is not necessary.

The RIFM PNEC is 0.1101 µg/L. The revised PEC/PNECs for EU and NA <1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 02/14/14.

10. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

* Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

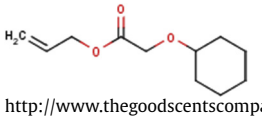
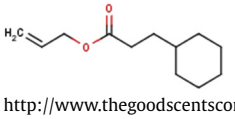
Conflict of interest

A.M. Api, S. Bhatia, L. Kromidas, S. La Cava, J.F. Lalko, A. Lapczynski, V.T. Politano, G. Ritacco, D. Salvito, J. Shen, B. Wall, D.K. Wilcox are employees of the Research Institute for Fragrance Materials, Inc. (RIFM); D. Belsito, M. Bruze, P. Calow, M.L. Dagli, W. Dekant, A.D. Fryer, D.C. Liebler, Y. Miyachi, T.W. Schultz, I.G. Sipes are members of the RIFM Expert Panel.

Transparency document

The Transparency document associated with this article can be found in the online version.

Appendix

	Target Material	Read across Material
Principal Name	Allyl (cyclohexyloxy)acetate	Allyl cyclohexanepropionate
CAS No.	68901-15-5	2705-87-5
Structure		
3D Structure	http://www.thegoodscentscompany.com/opl/68901-15-5.html	http://www.thegoodscentscompany.com/opl/2705-87-5.html
Read-across endpoint		• Genotoxicity • Repeated Dose • Devel/Repro
Molecular Formula	C11H18O3	C12H20O2
Molecular Weight	198.26	196.29
Melting Point (°C, EPISUITE)	22.95	17.28
Boiling Point (°C, EPISUITE)	254.86	254.19
Vapor Pressure (Pa @ 25 °C, EPISUITE)	2.8	2.906
Log Kow (KOWWIN v1.68 in EPISUITE)	2.72	4.47

(*continued on next page*)

Appendix (*continued*)

	Target Material	Read across Material
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	211.1	6.949
J_{max} (mg/cm^2/h, SAM)	39.19159014	13.69318113
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	3.514964	74.747452
Similarity (Tanimoto score) [a]		52%
Genotoxicity		
DNA binding (OASIS v1.1)	• No alert found	• No alert found
DNA binding (OECD)	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found
DNA alerts for Ames, MN, CA (OASIS v1.1)	• No alert found	• No alert found
In vitro mutagenicity (Ames test) alerts (ISS)	• No alert found	• No alert found
In vivo mutagenicity (Micronucleus) alerts (ISS)	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor
Oncologic classification (OECD)	• Not classified	• Not classified
Repeated Dose Toxicity		
Repeated dose (HESS)	Not categorized	Not categorized
Developmental and Reproductive Toxicity		
ER binding (OECD)	Non binder, without OH or NH2 group	Non binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (moderate reliability)	NON-Toxicant (moderate reliability)
Metabolism		
Rat liver S9 metabolism simulator (OECD)	See supplemental data 1	See supplemental data 2

[a] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).

Summary

There are insufficient toxicity data on Allyl (cyclohexyloxy)acetate (RIFM # 5937, CAS # 68901-15-5). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/Rationale

- Allyl cyclohexanepropionate (analog) was used as a read-across for Allyl (cyclohexyloxy)acetate (target) based on:
  - The target and analog both belong to the generic class of aliphatic esters, specifically, allyl esters.
  - Both have the same alcohol part and similar acid part.
  - The only difference is that the target is a cyclohexyloxy acetic acid ester, while the analog is a cyclohexane propionic acid ester. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the genotoxicity profiles are expected to be similar.
  - Both the target and the analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - Both materials are expected to be metabolized similarly. As per the OECD Toolbox both materials are predicted to have similar metabolites.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.fct.2015.03.016.

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