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RIFM fragrance ingredient safety assessment, allyl phenylacetate, CAS registry number 1797-74-6

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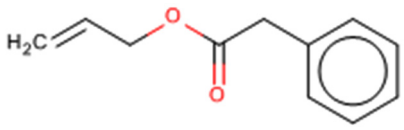

Abbreviation/Definition list:
2-Box model – a RIFM, Inc. proprietary in silico tool used to calculate fragrance air exposure concentration
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 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 25 mg/kg/day, based on a 13-week subchronic toxicity and 103-week chronic carcinogenicity studies in rats and mice on a read across analog, that resulted in a MOE of 47,170 considering 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

Human Health Safety Assessment
Genotoxicity: Not genotoxic (Wild et al., 1983)
Repeated Dose Toxicity: NOAEL = 25 mg/kg/day (NTP, 1985)
Developmental and Reproductive Toxicity: NOAEL = 50 mg/kg/day (ECHA REACH Dossier: Diallyl phthalate)
Skin Sensitization: Not a sensitization concern. Exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment: Persistence: Screening Level: 2.90 (EPISUITE ver 4.1)
Bioaccumulation: Screening Level: 39.6 L/kg (EPISUITE ver 4.1)
Ecotoxicity: Screening Level: LC50: 36.89 mg/L (Salvito et al., 2002)
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: LC50: 36.89 mg/L
RIFM PNEC is: 0.03689 μg/L
- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe NA; cleared at Screening Level

1. Identification

1. **Chemical Name:** Allyl phenylacetate
2. **CAS Registry Number:** 1797-74-6
3. **Synonyms:** Allyl phenylacetate, Allyl α-toluate, Benzeneacetic acid, 2-propenyl ester, 2-Propenyl phenylacetate
4. **Molecular Formula:** $C_{11}H_{12}O_2$
5. **Molecular Weight:** 176.22
6. **RIFM Number:** 706

2. Physical data

1. **Boiling Point:** 230 °C [FMA database], (calculated) 250.84 °C [EPI Suite]
2. **Flash Point:** > 212.00 °F TCC (>100.00 °C)*
3. **Log K_{OW}:** 2.93 [EPI Suite]
4. **Melting Point:** 20.18 °C [EPI Suite]
5. **Water Solubility:** 181.9 mg/L [EPI Suite]
6. **Specific Gravity:** 1.03600 @ 20.00 °C*
7. **Vapor Pressure:** 0.0164 mm Hg @ 20 °C [EPI Suite 4.0], 0.026 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Does not absorb in the region of 290–700 nm.
9. **Appearance/Organoleptic:** Colorless slightly viscous liquid with sweet honey-like, but faint, odor with sweet, fruity undertones. Honey-like taste.

* http://www.thegoodscentscompany.com/data/rw1002911.html, retrieved 03/21/14

3. Exposure

1. **Volume of Use (worldwide band):** <1 metric tons per year (IFRA, 2011)
2. **Average Maximum Concentration in Hydroalcoholics:** 0.002% (IFRA, 2008)

3. **97.5th Percentile:** 0.018% (IFRA, 2008)
4. **Dermal Exposure*:** 0.0005 mg/kg/day (IFRA, 2008)
5. **Oral Exposure:** Not available
6. **Inhalation Exposures**:** 0.000028 mg/kg/day (IFRA, 2008)
7. **Total Systemic Exposure (Dermal + Inhalation):** 0.00053 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 = 0.00053 mg/kg/day

5. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

Expert judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II	II	II

2. **Analogs Selected:**
   a. **Genotoxicity:** Allyl cinnamate (CAS # 1866-31-5)
   b. **Repeated Dose Toxicity:** Diallyl phthalate (CAS # 131-17-9)
   c. **Developmental and Reproductive Toxicity:** Diallyl phthalate (CAS # 131-17-9)
   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 phenylacetate is reported to occur in the following foods*:

Honey

* 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 phenylacetate does not present a concern for genetic toxicity.

9.1.1.1. Risk assessment. Allyl phenylacetate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity indicating a lack for genotoxic concern (RIFM, 2013). There are no further studies assessing its mutagenic activity. Read across analog, allyl cinnamate (CAS # 1866-31-5; see Section 5) was evaluated for mutagenicity in a bacterial reverse mutation assay (Ames) conducted in equivalent to OECD TG (Wild et al., 1983). *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to allyl cinnamate at concentrations up to 3.6 mg/plate in the presence and absence of metabolic activation. No significant increase in revertant colonies was observed (Wild et al., 1983). Under the conditions of the study, allyl cinnamate was considered not mutagenic in the Ames test.

There are no studies available assessing the clastogenic activity of allyl phenylacetate. Read across analog allyl cinnamate was assessed in an *in vivo* micronucleus test. 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 allyl cinnamate in olive oil. Compared to the olive-oil treated controls, no significant increase in the number of micronucleated polychromatic erythrocytes was observed at doses of 94, 188 and 282 mg/kg (Wild et al., 1983). Under the conditions of the study, allyl cinnamate was considered non-clastogenic in the *in vivo* MNT assay. Taken together, allyl cinnamate does not present a concern for genotoxic potential and this can be extended to allyl phenylacetate.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/25/14.

9.1.2. Repeated dose toxicity

The margin of exposure for allyl phenylacetate 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 phenylacetate. Read across material diallyl phthalate (CAS # 131-17-9; see Section 5) has been extensively studied for repeated dose toxicity. The NOAEL was determined to be 25 mg/kg/day from the 13-week subchronic toxicity study conducted in rats, based on liver effects (periportal hepatocellular necrosis and fibrosis; NTP, 1985). **Therefore, the MOE is equal to the diallyl phthalate NOAEL in mg/kg/day divided by the total systemic exposure, 25/0.00053 or 47170.**

Diallyl phthalate was found to be equivocal for carcinogenicity in female rats (mononuclear cell leukemia; NTP, 1985) and male and female mice (squamous cell papillomas of the forestomach and lymphomas; NTP, 1983). There was no evidence of carcinogenicity in male rats. The lowest oral dosage producing carcinogenesisin rats or mice was 100 mg/kg/day in rats (NTP, 1985). The total systemic exposure to allyl phenylacetate is 0.00053 mg/kg/day, which is more than 188,700 times lower than the lowest dose level in the animal studies. This MOE is considered adequate.

Additional References: Grundschober, 1977; RIFM, 1974; RIFM, 1980; Eigenberg et al., 1986; Auerbach et al., 2008; RIFM, 2006; Carpanini et al., 1978; Dunlap et al., 1958; OECD SIDS, 2005; ECHA REACH Dossier: Allyl alcohol; Butterworth et al., 1978; Dunlap et al., 1955; Smyth et al., 1951; Torkelson et al., 1959; Lake et al., 1975;

Berman et al., 1992; Lijinsky et al., 1987; Slott et al., 1985; McLaughlin et al., 1964; Slott et al., 1984; Jenkinson et al., 1990; Boggs et al., 1963; Zaitsev et al., 1974; Sherwin et al., 1919; Maganova et al., 1973; Zaitsev et al., 1975; Davies et al., 1956; Dawson et al., 1996; Hamers et al., 1989.

Literature Search and Risk Assessment Completed on: 02/21/14.

9.1.3. Developmental and reproductive toxicity

The margin of exposure for allyl phenylacetate 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 toxicity data on allyl phenylacetate. Read across material diallyl phthalate (CAS # 131-17-9; see Section 5) has an OECD 414 gavage developmental toxicity study that was conducted in rats. The NOAEL for developmental toxicity was determined to be 150 mg/kg/day, based on reduced fetal bodyweights and increased skeletal variations (ECHA REACH Dossier: Diallyl phthalate Exp Key Developmental toxicity/teratogenicity.001, accessed 02/21/14). These effects were observed at maternally toxic dosages. **Therefore, the MOE for developmental toxicity is equal to the diallyl phthalate NOAEL in mg/kg/day divided by the total systemic exposure, 150/0.00053 or 283019.**

There are no reproductive toxicity data on allyl phenylacetate. Read across material diallyl phthalate (CAS # 131-17-9) has an OECD 421 gavage reproduction/developmental toxicity screening test study that was conducted in rats. The NOAEL for reproductive toxicity was determined to be 50 mg/kg/day, based on mortality and dystocia (ECHA REACH Dossier: Diallyl phthalate Exp Key Toxicity to reproduction.001, accessed 02/21/14). **Therefore, the MOE for reproductive toxicity is equal to the diallyl phthalate NOAEL in mg/kg/day divided by the total systemic exposure, 50/0.00053 or 94340.**

Additional References: Grundschober, 1977; RIFM, 1974; RIFM, 1980; Eigenberg et al., 1986; Auerbach et al., 2008; RIFM, 2006; Carpanini et al., 1978; Dunlap et al., 1958; SIDS, 2005; ECHA REACH Dossier: Allyl alcohol; Butterworth et al., 1978; Dunlap et al., 1955; Smyth et al., 1951; Torkelson et al., 1959; Lake et al., 1975; Berman et al., 1992; Lijinsky et al., 1987; Slott et al., 1985; McLaughlin et al., 1964; Slott et al., 1984; Jenkinson et al., 1990; Boggs et al., 1963; Zaitsev et al., 1974; Sherwin et al., 1919; Maganova et al., 1973; Zaitsev et al., 1975; Davies et al., 1956; Dawson et al., 1996; Hamers et al., 1989.

Literature Search and Risk Assessment Completed on: 02/21/14.

9.1.4. Skin sensitization

Based on the available data and application of the DST, allyl phenylacetate does not present a significant concern for skin sensitization.

9.1.4.1. Risk assessment. Based on the available data and application of the DST, allyl phenylacetate does not present a significant concern for skin sensitization concern. 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 to allyl phenyl acetate was reported, however, due to significant toxicity observed during the course of the study and a limited dose response, the reliability of the calculated EC3 value is low (RIFM, 2011). In a human maximization test, positive results were also reported, but after retesting and controlling for allyl alcohol (a strong irritant) no reactions indicative of sensitization were observed (RIFM, 1975; RIFM, 1976). The positive responses to this and similar materials have been reported to be due to the strong irritant potential of allyl alcohol (Politano et al., 2006; Opdyke, 1977). The current IFRA Standard for this material limits the level of free allyl alcohol to less than 0.1%. Conservatively, due to the LLNA results, the reported exposure was benchmarked utilizing the reactive Dermal Sensitization Threshold (DST). The current dermal exposure from hydroalcoholic products, 0.002%, is below the DST for reactive materials when evaluated in QRA categories 3 and 4 (DST levels of 0.01% and 0.03%, respectively).

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/28/14.

9.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra, allyl phenylacetate does not present a concern for phototoxicity or photoallergenicity.

9.1.5.1. Risk assessment. Based on the available UV spectra, allyl phenylacetate does not absorb in the region of 290–700 nm and therefore would not present a concern for phototoxicity (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/28/14.

9.1.6. Local respiratory toxicity

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

9.1.6.1. Risk assessment. There are no inhalation data available on allyl phenylacetate. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.018%. 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 0.0017 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 (Respiratory Cramer Class II defaults to Class III) of 0.47 mg/person/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; Smyth et al., 1948; Torkelson et al., 1959; Dunlap et al., 1958; Dunlap et al., 1955; Zwart et al., 1992; Zissu, 1995; McCord, 1932; Luan et al, 2006; Engström, 1984; Li et al., 2012.

Literature Search and Risk Assessment Completed on: 02/28/14.

9.2. Environmental endpoint summary

9.2.1. Screening-level assessment

A screening level risk assessment of allyl phenylacetate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which 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 riskquotient (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 phenylacetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC <1).

A screening-level hazard assessment using EPISUITE ver 4.1 identified allyl phenylacetate as not persistent and not bio-accumulative 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 the most current VoU survey (2011), allyl phenylacetate does not present a risk to the aquatic compartment in the screening level assessment.

9.2.2.1. Biodegradation. No data available.

9.2.2.2. Ecotoxicity. No data available.

9.2.3. Other available data

Allyl phenylacetate has been pre-registered under REACH with no additional data at this time.

9.2.4. Risk assessment refinement

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**)	36.89 mg/L			1,000,000	0.03689 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.93	
Biodegradation factor used	0	
Dilution Factor	3	3
Regional volume of use tonnage band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

The RIFM PNEC is 0.03689 µg/L. The revised PEC/PNECs for EU and North America: Not Applicable. Allyl phenylacetate was cleared at the Screening Level 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: 02/24/14.

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.

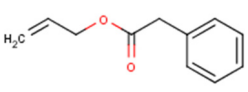
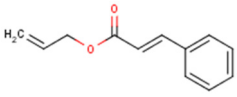
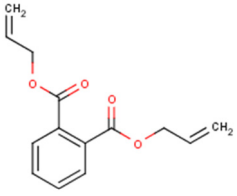
Conflict of interest

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 materials	
Principal name	Allyl phenylacetate	Allyl cinnamate	1,2-Benzenedicarboxylic acid, 1,2-di-2-propen-1-yl ester
CAS No.	1797-74-6	1866-31-5	131-17-9
Structure			
3D structure	http://www.thegoodscentscompany.com/opl/1797-74-6.html	http://www.thegoodscentscompany.com/opl/1866-31-5.html	http://www.thegoodscentscompany.com/opl/131-17-9.html
Read-across endpoint		•Genotoxicity	•Repeated Dose •Devel/Repro
Molecular Formula	C11H12O2	C12H12O2	C14H14O4
Molecular Weight	176.22	188.23	246.26
Melting Point (°C, EPISUITE)	20.18	29.72	15.82
Boiling Point (°C, EPISUITE)	250.84	272.90	309.72
Vapor Pressure (Pa @ 25 °C, EPISUITE)	3.466	0.00232	0.1547
Log K_{ow} (KOWWIN v1.68 in EPISUITE)	2.93	3.20	3.36

(*continued on next page*)

Appendix (*continued*)

	Target material	Read-across materials	
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	181.9	92.3	43.27
J_{max} (mg/cm^2/h, SAM)	34.26266079	18.51676058	2.230995275
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.883632	0.550904	0.039071
Similarity (Tanimoto score) [a]		63%	50%
Genotoxicity			
DNA binding (OASIS v1.1)	• No alert found	• No alert found	
DNA binding (OECD)	• Michael addition • Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals • Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals >> Arenes	• 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	• Acrylate Reactive Functional Groups	
Repeated Dose Toxicity			
Repeated dose (HESS)	Not categorized		Phthalate esters (Testicular toxicity) Rank C
Developmental and Reproductive toxicity			
ER Binding by OECD QSAR Tool Box (3.1)	Non binder, without OH or NH2 group		Non binder, without OH or NH2 group
Developmental Toxicity Model by CAESAR v2.1.6	NON-Toxicant (low reliability)		Toxicant (moderate reliability)
Metabolism			
Rat liver S9 metabolism simulator (OECD)	See supplemental data 1	See supplemental data 2	See supplemental data 3

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

Summary

There are insufficient toxicity data on Allyl phenylacetate (RIFM # 706, CAS # 1797-74-6). 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)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/Rationale

- Allyl cinnamate (analog) was used as a read-across for Allyl phenylacetate (target) based on:
  - The target and analog belong to the generic class of aliphatic esters, specifically, allyl esters.
  - The target and analog have the same alcohol part and similar carboxylic acid part.
  - The key difference between target and analog are that the target is a phenylacetic acid ester, while the analog is a cinnamic 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.
  - Although the target shows additional structural alert in OECD DNA binding, these come from a very specific and limited scope of chemicals of different structures. Based on consensus in silico predictions, the target and the read across materials show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox both materials are predicted to have similar metabolites.
- 1,2-Benzenedicarboxylic acid, 1,2-di-2-propen-1-yl ester (analog) was used as a read-across for Allyl phenylacetate (target) based on:
  - The target and analog belong to the generic class of aliphatic esters, specifically, allyl esters.
  - The target and analog have the same alcohol part and similar carboxylic acid part.

- The key difference between target and analog are that the target is a phenylacetic acid ester, while analog is a phthalic acid ester, in which two carboxylic acids are all esterized with two allyl alcohols. The target is more reactive in nuclear receptor bindings and therefore is considered as the worst scenario.
- The analog shows alerts for Repeated Dose (HESS) Categorization and is predicted as toxicant in CAESAR, while the target does not.
- The target and analog are expected to metabolize via similar pathway. 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.2015.03.018.

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