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Short review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, propyl phenethyl acetal, CAS Registry Number 7493-57-4

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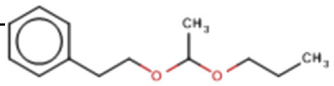


Abbreviation/Definition List:

2-Box Model- a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
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; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach.
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA- European Chemicals Agency
EU- Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD- Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA- North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
NOEL- No Observed Effect Level
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
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
WOE- Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits 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 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 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
The material (propyl phenethyl acetal) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the target material (propyl phenethyl acetal) and from the read across analog acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7) show that propyl phenethyl acetal is not genotoxic. Data from the target material (propyl phenethyl acetal) and the read across analog phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) show that propyl phenethyl acetal does not have skin sensitization potential. The developmental, reproductive, repeated dose, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoints were evaluated, 3-methyl-2-pentylcyclopentan-1-one was found not to be a PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2000a; RIFM, 2015a)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not sensitizing. (RIFM, 2016b; RIFM, 1984; RIFM, 1968; RIFM, 1964)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening Level: 2.66 (Biowin 3) (US EPA, 2012a)
Bioaccumulation: Screening Level: 81.8 l/kg (US EPA, 2012a)

(*continued on next page*)

(*continued*)

Ecotoxicity: Screening Level: 48-hr *Daphnia magna* LC50: 6.068 mg/l (US EPA, 2012a)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards.

Risk Assessment:
Screening-Level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-hr *Daphnia magna* LC50: 6.068 mg/l (US EPA, 2012a)
RIFM PNEC is: 0.6068 μg/l
•**Revised PEC/PNECs (2011 IFRA Volume of Use)**: North America and Europe: <1

1. Identification

1. **Chemical Name:** Propyl phenethyl acetal
2. **CAS Registry Number:** 7493-57-4
3. **Synonyms:** Acetaldehyde phenethyl propyl acetal; Acetal R; Benzene, [2-(1-propoxyethoxy)ethyl]-; 1-Phenethoxy-1-propoxyethane; (2-(1-Propoxyethoxy)ethyl)benzene; Propyl phenethyl acetal; ｱｾﾄｱﾙﾃﾞﾋﾄﾞ-ﾌﾛﾛﾋﾞﾙ-(2-ﾌｴﾆﾙ-ｴﾁﾙ)ｱｾﾀｰﾙ; [2-(1-Propoxyethoxy)ethyl]benzene; Resedafol-Corps 302
4. **Molecular Formula:** $C_{13}H_{20}O_2$
5. **Molecular Weight:** 208.3
6. **RIFM Number:** 68

2. Physical data

1. **Boiling Point:** 272.67 °C [US EPA, 2012a]
2. **Flash Point:** >200 °F;CC [FMA database], >93 °C [GHS]
3. **Log K_{OW}:** 3.4 [US EPA, 2012a]
4. **Melting Point**: 32.27 °C [US EPA, 2012a]
5. **Water Solubility:** 49.14 mg/l [US EPA, 2012a]
6. **Specific Gravity:** 0.955 [FMA]
7. **Vapor Pressure:** 0.00398 mmHg @ 20 °C [US EPA, 2012a], 0.009 mm Hg @ 20 °C [FMA], 0.00708 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid with a powerful, ethereal, green-herbal leafy odor.

3. Exposure

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.014% (RIFM, 2015b)
3. **Inhalation Exposure*:** 0.000077 mg/kg/day or 0.0055 mg/day (RIFM, 2015b)
4. **Total Systemic Exposure**:** 0.00050 mg/kg/day (RIFM, 2015b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 et al., 2015, 2017; Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I*	II	II

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was also determined using expert judgment based on the Cramer decision tree (Cramer et al., 1976). See Appendix below for further details.

2. Analogs selected
   a. **Genotoxicity:** Acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** Phenylacetaldehyde dimethyl acetal (CAS # 101-48-4)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read across Justification:** See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Propyl phenethyl acetal 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.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 07/14/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, propyl phenethyl acetal does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Propyl phenethyl acetal was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013). The mutagenic activity of propyl phenethyl acetal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with propyl phenethyl acetal in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2000a). Under the conditions of the study, propyl phenethyl acetal was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of propyl phenethyl acetal; however, read across can be made to acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7; see Section 5). The clastogenic activity of acetaldehyde ethyl phenylethyl acetal 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 for 4 and 24 h with acetaldehyde ethyl phenylethyl acetal in DMSO at concentrations up to 960 μg/ml in the presence and absence of S9 metabolic activation. Acetaldehyde ethyl phenylethyl acetal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2015a). Under the conditions of the study, acetaldehyde ethyl phenylethyl acetal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to propyl phenethyl acetal.

Based on the data available, propyl phenethyl acetal does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 7/5/2016.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on propyl phenethyl acetal or any read across materials. The total systemic exposure to propyl phenethyl acetal is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on propyl phenethyl acetal or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to propyl phenethyl acetal (0.50 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/13/2017.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on propyl phenethyl acetal or any read across materials. The total systemic exposure to propyl phenethyl acetal is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on propyl phenethyl acetal or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to propyl phenethyl acetal (0.50 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/13/2017.

10.1.4. Skin sensitization

Based on the existing data and read across to phenylacetaldehyde dimethyl acetal (CAS # 101-48-4), propyl phenethyl acetal does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data and read across to phenylacetaldehyde dimethyl acetal (CAS # 101-48-4; see section 5), propyl phenethyl acetal does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), read across phenylacetaldehyde dimethyl acetal was found to be non-sensitizing up to 100% (RIFM, 2016b). In guinea pig studies, weight of evidence suggests both propyl phenethyl acetal and phenylacetaldehyde dimethyl acetal are not sensitizers (RIFM, 1984; RIFM, 1968; RIFM, 1982b; RIFM, 1982a). Similarly, in confirmatory human repeated insult patch tests (HRIPT), 0.5% or 388 μg/cm^2 propyl phenethyl acetal in ethanol (RIFM, 1964) or 1380μg/cm^2 of phenylacetaldehyde dimethyl acetal in 95% ethanol (RIFM, 1965), produced no reactions indicative of sensitization in any of the volunteers. Additionally, in human maximization tests no sensitization reactions were observed when 5% or 3450 μg/cm^2 propyl phenethyl acetal in petrolatum (RIFM, 1979) or 2% or 1380μg/cm^2 of phenylacetaldehyde dimethyl acetal in petrolatum (RIFM, 1971) was used for induction and challenge. Based on the weight of evidence from structural analysis, animal models, human studies and read across, propyl phenethyl acetal does not present a concern for skin sensitization.

Additional References: RIFM, 1976; Klecak, 1979, 1985

Literature Search and Risk Assessment Completed on: 01/26/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, propyl phenethyl acetal would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for propyl phenethyl acetal in experimental models. The UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is

well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of absorbance, propyl phenethyl acetal does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/17/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, propyl phenethyl acetal, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on propyl phenethyl acetal. Based on the Creme RIFM model, the inhalation exposure is 0.0055 mg/day. This exposure is 255 times lower than the Cramer Class I TTC value of 1.4 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.

Additional References: None.

Literature Search and Risk Assessment Completed on: 12/15/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of methylcyclooctyl carbonate 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 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 (US EPA, 2012b) (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). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range.

Following the RIFM Environmental Framework, methylcyclooctyl carbonate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.1 (US EPA, 2012a) did not identify methylcyclooctyl carbonate as either being possibly persistent nor 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 EPI Suite v4.1).

10.2.2. Risk assessment

Based on current Volume of Use (2011), propyl phenethyl acetal presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. RIFM, 2000b: A *Daphnia magna* acute toxicity study was conducted according to the Council Directive 92/69/EEC C.2 (92) method. The 48-h EC50 of the test material was reported to be 12 mg/l (arithmetic mean).

Other available data:

Propyl phenethyl acetal has been pre-registered for REACH with no additional data at this time.

10.2.3. 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)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	17.01 mg/l			1,000,000	0.01701 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	9.387 mg/l	6.068 mg/l	7.725 mg/l	10,000	0.6068 µg/l	Neutral Organic SAR

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.4	3.4
Biodegradation Factor Used	0.1	0.1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.6068 μg/l. The revised PEC/PNECs for EU and NA are <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: 1/6/16.

11. 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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.09.030.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.09.030.

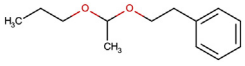
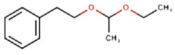
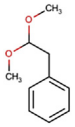
Appendix

Read across justification

Methods

The read across analogs were identified following the strategy for structuring and reporting a read across prediction of toxicity described in Schultz et al. (2015) and is consistent with the guidance provided by the OECD on the reporting of the defined approached used within the Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical read across assessment framework (ECHA, 2016).

- In essence, materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster was examined. Finally, appropriate read across analogs from the cluster were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical-chemical properties of the target substance and the read across analog were calculated using EPI Suite™ v4.11 (US EPA, 2012a).
- 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 generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target material	Read across material	
Principal Name	Propyl phenethyl acetal	Acetaldehyde ethyl phenylethyl acetal	Phenylacetaldehyde dimethyl acetal
CAS No.	7493-57-4	2556-10-7	101-48-4
Structure			
Similarity (Tanimoto score)		0.62	0.52
Read across endpoint		•Genotoxicity	•Skin sensitization
Molecular Formula	$C_{13}H_{20}O_2$	$C_{12}H_{18}O_2$	$C_{10}H_{14}O_2$
Molecular Weight	208.3	194.27	166.22
Melting Point (°C, EPISUITE)	32.27	21.75	−0.08
Boiling Point (°C, EPISUITE)	272.67	255.94	219.76
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.944	2.64	17.7
Log Kow (KOWWIN v1.68 in EPISUITE)	3.4	3.3[1]	2.23[2]
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	49.14	152.3	1439

(continued on next page)

(*continued*)

	Target material	Read across material	
J_{max} (mg/cm^2/h, SAM)	20.322	60.202	151.627
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.27E-005	9.55E-006	5.42E-006
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition	• Michael addition	
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found	
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Skin Sensitization			
Protein binding by OASIS v1.1	• No alert found		• No alert found
Protein binding by OECD	• No alert found		• No alert found
Protein binding potency	• Not possible to classify		• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found		• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (low reliability)		• Sensitizer (moderate reliability)
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See supplemental data 1	See supplemental data 2	See supplemental data 3

1. RIFM, 2002.
2. RIFM, 2016a.

Summary

There are insufficient toxicity data on propyl phenethyl acetal (CAS # 7493-57-4). Hence, *in silico* evaluation was conducted to determine read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, analogs acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7) and phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) were identified as read across materials with data for their respective toxicity endpoint.

Conclusion/rationale

- Acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7) could be used as a read across analog for the target material propyl phenethyl acetal (CAS # 7493-57-4) for the genotoxicity endpoint.
  - The target substance and the read across analog are structurally similar and belong to the structural class of acetals. The target substance and the read across analog share an acetal structure.
  - The key difference between the target substance and the read across analog is that they have different alkyl substituents on the acetal. The differences in structure between the target substance and the read across analog do not raise additional structural alerts, so, the structural differences are not relevant from a toxicological endpoint perspective.
  - Similarity between the target substance and the read across analog is indicated by the Tanimoto score provided in the table above. The Tanimoto score is mainly driven by the acetal group and alkyl chain on the alcohol portion. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicological endpoint perspective.
  - The target substance and the read across analog have similar physical-chemical properties. Any differences in physical-chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for the genotoxicity endpoint.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for the genotoxicity endpoint are consistent between the target substance and the read across analog as seen in the table above.
  - The target substance and the read across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - The structural alerts for the genotoxicity endpoint are consistent between the metabolites of the read across analog and the target substance.
- Phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) could be used as a read across analog for the target material propyl phenethyl acetal (CAS # 7493-57-4) for the skin sensitization endpoint.
  - The target substance and the read across analog are structurally similar and belong to the structural class of acetals.
  - The target substance and the read across analog share an acetal structure.
  - The key difference between the target substance and the read across analog is that they have different substitutions on the acetal. The differences in structure between the target substance and the read across analog do not raise additional structural alerts, so, the structural differences are not relevant from a toxicological endpoint perspective.
  - Similarity between the target substance and the read across analog is indicated by the Tanimoto score provided in the table above. The Tanimoto score is mainly driven by the acetal group and alkyl chain on the alcohol portion. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicological endpoint perspective.
  - The target substance and the read across analog have similar physical-chemical properties. Any differences in some of the physical-chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for the skin sensitization endpoint.
  - Structural alerts for the skin senzitization endpoint are consistent between the target substance and the read across analog as seen in the table above. According to the CAESAR v.2.1.6 model, the read across analog and the target material are predicted to be sensitizers, so the skin sensitization profile of both of the substances is expected to be same. Negative sensitization data for the read across override the prediction.

- The target substance and the read across analog are expected to be metabolized similarly as shown by the metabolism simulator.
- The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read across analog and the target substance.

Explanation of cramer classification

Q1. Normal constituent of the body? **No**
Q2. Contains functional groups associated with enhanced toxicity? **No**
Q3. Contains elements other than C, H, O, N, and divalent S? **No**
Q4. Elements not listed in Q3 occurs only as a Na, K, Ca, Mg, N salt, sulfamate, sulfonate, sulfate, hydrochloride? **No**
Q4. Elements not listed in Q3 occurs only as a Na, K, Ca, Mg, N salt, sulfamate, sulfonate, sulfate, hydrochloride? **No**
Q6. Benzene derivative with certain substituents? **No**
Q7. Heterocyclic? **No**
Q16. Common terpene? **No**
Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open chain? **Yes**
Q20. Is the structure a linear or simply branched (I) aliphatic (A) compound containing any one or combination of the following functional groups: four or less of alcohol, aldehyde, carboxylic acid or esters and or one or more of the following: acetal, ketone or ketal (not both), mercaptan, sulphide, thioester, polyoxyethylene or primary or tertiary amine? **Yes**
Q21. 3 or more different functional groups? **No**
Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity) **No**

Class Low (Class I).

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