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Short review

RIFM fragrance ingredient safety assessment, phenylacetaldehyde diethyl acetal, CAS Registry Number 6314-97-2

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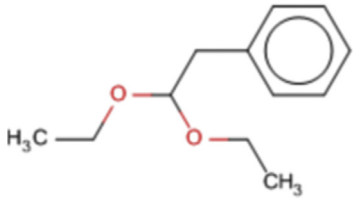


Abbreviation list:
2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data 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
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

RIFM's Expert Panel* 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 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 conditions is supported by existing information.
The material (phenylacetaldehyde diethyl acetal) was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from read across analog acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7) show that phenylacetaldehyde diethyl acetal is not genotoxic. Data from read across analog phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) show that phenylacetaldehyde diethyl acetal does not have skin sensitization potential. The repeated dose, developmental and reproductive, 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 UV spectra. The environmental endpoints were evaluated, phenylacetaldehyde diethyl acetal was found not to be 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, 1981; 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, 1982a; RIFM, 1982b; RIFM, 1965; RIFM, 1971)
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: 2.7 (Biowin 3)	(US EPA, 2012a)
Bioaccumulation: Screening Level: 38.8 L/kg	(US EPA, 2012a)
Ecotoxicity: Screening Level: Fish LC50: 42.33 mg/L	(US EPA, 2012a)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	

(*continued*)

Screening-Level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 42.33 mg/L (US EPA, 2012a)
RIFM PNEC is: 0.04233 μg/L
- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: not applicable; cleared at screening level

1. Identification

1. **Chemical Name:** Phenylacetaldehyde diethyl acetal
2. **CAS Registry Number**: 6314-97-2
3. **Synonyms:** Benzene, (2,2-diethoxyethyl)-; (2,2-Diethoxyethyl) benzene; 1,1-Diethoxy-2-phenylethane; Phenylacetaldehyde diethyl acetal; Benzeneacetaldehyde, diethyl acetal
4. **Molecular Formula**: $C_{12}H_{18}O_2$
5. **Molecular Weight**: 194.27
6. **RIFM Number**: 5123

2. Physical data

1. **Boiling Point:** 255.94 °C [EPI Suite]
2. **Flash Point:** 167.00 °F TCC (75 °C)*
3. **Log K_{OW}**: 2.91 [EPI Suite]
4. **Melting Point**: 21.75 °C [EPI Suite]
5. **Water Solubility:** 152.3 mg/L [EPI Suite]
6. **Specific Gravity**: Not Available
7. **Vapor Pressure:** 0.0124 mmHg @ 20 °C [EPI Suite 4.0], 0.0198 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** A colorless to pale, yellow, clear liquid with a medium, green, fresh, bluebell, almond, sweet, lime blossom odor.*

*http://www.thegoodscentscompany.com/data/rw1049021.html#toorgano, retrieved 9/9/2015.

3. Exposure

1. **Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.0024% (RIFM, 2015b)
3. **Inhalation Exposure*:** 0.0000095 mg/kg/day or 0.00064 mg/day (RIFM, 2015b)
4. **Total Systemic Exposure**:** 0.000038 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; and 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; and 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., 1978). 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

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

Phenylacetaldehyde diethyl acetal is reported to occur in the following foods*:

Apple brandy (Calvados)
Grape brandy
Sherry
Tequila (Agave tequilana)
Wine

*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

None.

8. Reach dossier

Pre-registered for 2010; no dossier available as of 7/21/17.

9. Summary

9.1. Human health endpoint summaries

9.1.1. Genotoxicity

Based on current existing data, phenylacetaldehyde diethyl acetal does not present a concern for genotoxicity.

9.1.1.1. Risk assessment. Phenylacetaldehyde diethyl acetal was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). There are no data assessing the mutagenic activity of phenylacetaldehyde diethyl acetal however, read across can be made to acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7; see Section 5). The mutagenic activity of acetaldehyde ethyl phenylethyl acetal has been evaluated in a bacterial reverse mutation assay conducted according to a protocol similar to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with acetaldehyde ethyl phenylethyl acetal in methanol at concentrations up to 500 μg/plate. No increases in the mean number of revertant colonies were observed at any dose tested in the presence or absence of S9 (RIFM, 1981). Under the conditions of the study, acetaldehyde ethyl phenylethyl acetal was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of phenylacetaldehyde diethyl 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 with acetaldehyde ethyl phenylethyl acetal in DMSO (dimethyl sulfoxide) at concentrations up to 960 μg/ml in the presence and absence of metabolic activation (S9) at the 4 h and 24 h timepoints. 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.

Based on the data available, acetaldehyde ethyl phenylethyl acetal does not present a concern for genotoxic potential and this can be extended to phenylacetaldehyde diethyl acetal.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/05/2016.

9.1.2. Repeated dose toxicity

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

9.1.2.1. Risk assessment. There are no repeated dose toxicity data on phenylacetaldehyde diethyl acetal or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to phenylacetaldehyde diethyl acetal (0.038 μg/kg/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: 10/14/2016.

9.1.3. Developmental and reproductive toxicity

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

9.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on phenylacetaldehyde diethyl acetal or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to phenylacetaldehyde diethyl acetal (0.038 μg/kg/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: 10/14/2016.

9.1.4. Skin sensitization

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

9.1.4.1. Risk assessment. There are no skin sensitization studies available for phenylacetaldehyde diethyl acetal. Based on the existing data and read across material phenylacetaldehyde dimethyl acetal (CAS# 101-48-4; see Section 5), phenylacetaldehyde diethyl 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; OECD toolbox v3.4; Toxtree 2.6.13). In a murine local lymph node assay (LLNA), read-across material phenylacetaldehyde dimethyl acetal was found to be non-sensitizing up to 100% (RIFM, 2016). In guinea pig studies, weight of evidence suggests phenylacetaldehyde dimethyl acetal is not a sensitizer (RIFM, 1982a; RIFM, 1982b). In a confirmatory human maximization test, no skin sensitization reactions were observed with read across material phenylacetaldehyde dimethyl acetal (RIFM, 1971). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 1380μg/cm^2 of read across material phenylacetaldehyde dimethyl acetal in 95% ethanol, no reactions indicative of sensitization were observed in any of the 39 volunteers (RIFM, 1965). Based on the weight of evidence from structural analysis, animal and human studies, and read across material phenylacetaldehyde dimethyl acetal, phenylacetaldehyde diethyl acetal does not present a concern for skin sensitization.

Additional References: Klecak, 1979; Klecak, 1985.

Literature Search and Risk Assessment Completed on: 10/21/2016.

9.1.5. Phototoxicity/photoallergenicity

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

9.1.5.1. Risk assessment. There are no phototoxicity studies available for phenylacetaldehyde diethyl acetal in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. 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 the lack of absorbance, phenylacetaldehyde diethyl acetal does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/08/2016.

9.1.6. Local respiratory toxicity

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

9.1.6.1. Risk assessment. There are limited inhalation data available on phenylacetaldehyde diethyl acetal. Based on the Creme RIFM model, the inhalation exposure is 0.00064 mg/day. This exposure is 2188 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: RIFM, 1997.

Literature Search and Risk Assessment Completed on: 10/20/2016.

9.2. Environmental endpoint summary

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	42.33 mg/L			1,000,000	0.04233 µg/L	

9.2.1. Screening-level assessment

A screening level risk assessment of phenylacetaldehyde diethyl acetal 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, phenylacetaldehyde diethyl acetal 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 did not identify phenylacetaldehyde diethyl acetal 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 EPISUITE ver.4.1).

9.2.2. Risk assessment

Based on the current Volume of Use (2011), phenylacetaldehyde diethyl acetal 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.

9.2.2.3. Other available data. Phenylacetaldehyde diethyl acetal has been pre-registered for REACH with no additional data at this time.

9.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in µg/L).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.91	2.91
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<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 0.04233 µg/L. The revised PEC/PNECs for EU and NA: Not applicable: cleared at screening level and therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 01/06/2016.

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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.08.039.

Transparency document

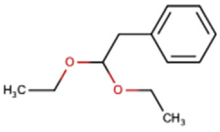
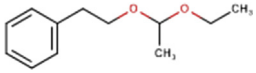
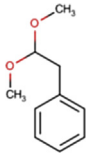
Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.08.039.

Appendix

Read across justification

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, 2012a,b).
- The Jmax 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 (v3.4) (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 (v.2.1.6) (Cassano et al., 2010).
- Protein binding were 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	Phenylacetaldehyde diethyl acetal	Acetaldehyde ethyl phenylethyl acetal	Phenylacetaldehyde dimethyl acetal
CAS No.	6314-97-2	2556-10-7	101-48-4
Structure			
Similarity (Tanimoto score)[1]		0.759	0.924
Read across endpoint		• Genotoxicity	• Skin sensitization
Molecular Formula	$C_{12}H_{18}O_2$	$C_{12}H_{18}O_2$	$C_{10}H_{14}O_2$
Molecular Weight	194.27	194.27	166.22
Melting Point (°C, EPISUITE)	21.75	21.75	−0.08
Boiling Point (°C, EPISUITE)	255.94	255.94	219.76
Vapor Pressure (Pa @ 25°C, EPISUITE)	2.64	2.64	17.7
Log Kow (KOWWIN v1.68 in EPISUITE)	2.91	3.3[1]	2.3[2]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	152.3	152.3	1439
J_{max} (mg/cm²/h, SAM)	27.405	60.202	169.043
Henry's Law (Pa·m³/mol, Bond Method, EPISUITE)	9.55E-006	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 (genotox and non-genotox) 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	

(*continued*)

	Target material	Read across material	
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, 1999.

Summary

There are insufficient toxicity data on phenylacetaldehyde diethyl acetal (CAS # 6314-97-2). Hence, *in-silico* evaluation was conducted by determining suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogs acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7) and phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) were identified as proper read across materials with data for their respective toxicological endpoints.

Conclusion/Rationale

- Acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7) could be used as a structurally similar read across analog for target material phenylacetaldehyde diethyl acetal (CAS # 6314-97-2) for the genotoxicity endpoint.
  - o The target substance and the read across analog are structurally similar and belong to a class of phenylacetaldehyde acetals.
  - o The target substance and the read across analog have an organic functional group acetal common among them.
  - o The key difference between the target substance and the read across analog is that the target substance is an acetal of phenethylacetaldehyde and ethanol while the read across analog is an acetal of acetaldehyde, ethanol and phenethyl alcohol.
  - o The target substance and the read across analog have a Tanimoto score as mentioned in the above table. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxicological endpoint perspective.
  - o The target substance and the read across analog have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for the genotoxicity endpoint.
  - o 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.
  - o The target substance and the read across analog are expected to be metabolized similarly as shown by metabolism simulator. The read across analog has additional metabolites due to the presence of a phenylethyl substructure on the alcohol side. These additional metabolites do not raise alerts for the genotoxicity endpoint.
  - o The structural differences between the target substance and the read across analog are deemed to be toxicologically insignificant for the genotoxicity endpoint.
- Phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) could be used as a structurally similar read across analog for target material phenylacetaldehyde diethyl acetal (CAS # 6314-97-2) for the skin sensitization endpoint.
  - o The target substance and the read across analog are structurally similar and belong to a class of aryl acetals.
  - o The target substance and the read across analog have a phenethyl aldehyde portion common among them.
  - o The key difference between the target substance and the read across analog is that the target is an acetal of phenethylacetaldehyde and ethanol while the read across is an acetal of phenethylacetaldehyde and methanol.
  - o The target substance and the read across analog have a Tanimoto score as mentioned in the above table. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxicological endpoint perspective.
  - o 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.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for the skin sensitization endpoint are consistent between the target substance and the read across analog.
  - o According to the CAESAR model, both the read across analog and the target substance are predicted to be sensitizers. Data described above in the skin sensitization section show that the read across material does not present a concern for skin sensitization. Therefore, the prediction is superseded by the data.
  - o The target substance and the read across analog are expected to be metabolized similarly as shown by metabolism simulator.
  - o The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read across analog and the target substance.
  - o The structural differences between the target substance and the read across analog are deemed to be toxicologically insignificant for skin sensitization endpoint.

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, divalent S **No**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate **No**

Q6. Benzene derivative with certain substituents **No**
Q7. Heterocyclic **No**
Q16. Common terpene **No**
Q17. Readily hydrolysed to a common terpene **No**
Q19. Open chain **No**
Q23. Aromatic **Yes**
Q27. Rings with substituents **Yes**
Q28. More than one aromatic ring **No**
Q30. Aromatic Ring with complex substituents **Yes**
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? **Yes**
Q18. One of the following category (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)

References

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., Renkers, 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.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

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., et al., 2010, July. CAESAR Models for Developmental Toxicity. In Chemistry Central Journal (Vol. 4, No. S1, p. S4). Springer International Publishing.

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.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Cosmet. Toxicol. 16 (3), 255–276.

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), 2011. Volume of Use Survey. February 2011.

Klecak, G., 1979. The Open Epicutaneous Test (OET), a Predictive Test Procedure in the Guinea Pig for Estimation of Allergenic Properties of Simple Chemical Compounds, Their Mixtures and of Finished Cosmetic Preparations. International Federation Societies Cosmetic Chemists, 9/18/79.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. In: problems in Dermatology. Curr. Problems Dermatol. 14, 152–171.

OECD, 2012. The OECD QSAR Toolbox v. 3.1. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1965. Repeated Insult Patch Test with Phenylacetaldehyde Dimethyl Acetal in Humans. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 54723.

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

RIFM (Research Institute for Fragrance Materials, Inc.), 1981. Evaluation of Acetaldehyde Ethyl Phenylethyl Acetal in the Salmonella/Microsome Mutagenicity Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 45957.

RIFM (Research Institute for Fragrance Materials, Inc.), 1982a. Guinea pig Skin Sensitisation Test with Phenylacetaldehyde Dimethyl Acetal. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 46686.

RIFM (Research Institute for Fragrance Materials, Inc.), 1982b. Guinea pig Skin Sensitisation Test with Phenylacetaldehyde Dimethyl Acetal (PADMA B). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 46687.

RIFM (Research Institute for Fragrance Materials, Inc.), 1997. Investigation of Oxidation Gases from Paraffin Aromatic Candles in Toxicological Relevance to Classes of Damaging Materials. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from The Union of German Candle Manufacturers. RIFM report number 18011.

RIFM (Research Institute for Fragrance Materials, Inc.), 1999. Partition Coefficient N-octanol/water of Phenylacetaldehyde Dimethyl Acetal (Viridine). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 51521.

RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Partition Coefficient N-octanol/water of Acetaldehyde Ethyl Phenylethyl Acetal (Acetal E). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 51425.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Phenylacetaldehyde Diethyl Acetal in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 66168.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015a. Acetaldehyde Ethyl Phenylethyl Acetal: Micronucleus Test in Human Lymphocytes in Vitro. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 68491.

RIFM (Research Institute for Fragrance Materials), 2015b. Use Level Survey. May 2015.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016. Phenylacetaldehyde Dimethyl Acetal: Skin Sensitization: Local Lymph Node Assay in Mice. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 70567.

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.

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., et al., 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.

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. v. 4.0–4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft® Windows. v1.11. United States Environmental Protection Agency, Washington, DC, USA.