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Short review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, acetaldehyde ethyl phenylethyl acetal, CAS Registry Number 2556-10-7

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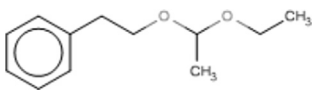

Abbreviation/Definition List:
2-Box Model- a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor

(*continued on next page*)

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(*continued*)

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 (acetaldehyde ethyl phenylethyl acetal) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that acetaldehyde ethyl phenylethyl acetal is not genotoxic. Data from the target material (acetaldehyde ethyl phenylethyl acetal) and the read across material, phenylacetaldehyde dimethyl acetal (CAS # 101-48-4), show that acetaldehyde ethyl phenylethyl acetal does not have skin sensitization potential. The reproductive, repeated dose and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.030, 0.030 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on data on acetaldehyde ethyl phenylethyl acetal and UV spectra. The environmental endpoints were evaluated, acetaldehyde ethyl phenylethyl 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. (RFIM, 1981b; 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; RFIM, 1980a; RFIM, 1982a; RIFM, 1964)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.
(UV Spectra, RIFM DB; RFIM, 1981a; RFIM, 1980b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 59% (OECD 302C) (RFIM, 2002b)
Bioaccumulation: Screening Level: 38.8 l/kg (US EPA, 2012a)
Ecotoxicity: Screening Level: 48-hr *Daphnia magna* LC50: 14.93 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: 14.93 mg/l (US EPA, 2012a))
RIFM PNEC is: 1.493 μg/l

- **Revised PEC/PNECs (2011 IFRA Volume of Use)**: North America and Europe: <1

1. Identification

1. **Chemical Name:** Acetaldehyde ethyl phenylethyl acetal
2. **CAS Registry Number:** 2556-10-7
3. **Synonyms:** Acetaldehyde ethyl phenylethyl acetal; Acetaldehyde ethyl 2-phenylethyl acetal; Acetaldehyde ethyl phenethyl acetal; Benzene, [2-(1-ethoxyethoxy)ethyl]-; (2-(1-Ethoxyethoxy)ethyl)benzene; Hyacinth body; Verotyl; [2-(1-Ethoxyethoxy)ethyl]benzene; Ethyl phenethyl acetal; Efetaal; Acetal E; Phenoxyacetaldehyde diethyl acetal
4. **Molecular Formula:** $C_{12}H_{18}O_2$
5. **Molecular Weight:** 194.27
6. **RIFM Number:** 596

2. Physical data

1. **Boiling Point:** >200 °C [FMA database], 255.94 °C [US EPA, 2012a]
2. **Flash Point:** >93 °C [GHS], >200 °F; CC [FMA database]
3. **Log KOW:** 3.3 @ 35 °C [RFIM, 2002c], 2.91 [US EPA, 2012a]
4. **Melting Point:** 21.75 °C [US EPA, 2012a]
5. **Water Solubility:** 152.3 mg/l [US EPA, 2012a]
6. **Specific Gravity:** 0.957 [FMA database], 0.9595 @ 25/25 °C [RIFM]
7. **Vapor Pressure:** 0.0124 mm Hg @ 20 °C [US EPA, 2012a], 0.02 mm Hg @ 20 °C [FMA database], 0.0198 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 leafy-green, delicately rosy and sweet odor

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.067% (RIFM, 2015b)
3. **Inhalation Exposure*:** 0.00034 mg/kg/day or 0.025 mg/day (RIFM, 2015b)
4. **Total Systemic Exposure**:** 0.0016 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	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:** None
   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)

Acetaldehyde ethyl phenylethyl acetal is reported to occur in the following foods*:

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.

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, acetaldehyde ethyl phenylethyl acetal

does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Acetaldehyde ethyl phenylethyl 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 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 tested dose in the presence or absence of S9 (RFIM, 1981b). Under the conditions of the study, acetaldehyde ethyl phenylethyl acetal was not mutagenic in the Ames test.

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 (dimethyl sulfoxide) 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.

Based on the data available, acetaldehyde ethyl phenylethyl acetal does not present a concern for genotoxic potential.

Additional References: None

Literature Search and Risk Assessment Completed on: 7/3/2016

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on acetaldehyde ethyl phenylethyl acetal or any read across materials. The total systemic exposure to acetaldehyde ethyl phenylethyl 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 acetaldehyde ethyl phenylethyl acetal or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to acetaldehyde ethyl phenylethyl acetal (1.6 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: RIFM, 1976a; RIFM, 1976b.

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 acetaldehyde ethyl phenylethyl acetal or any read across materials. The total systemic exposure to acetaldehyde ethyl phenylethyl 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 acetaldehyde ethyl phenylethyl acetal or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to acetaldehyde ethyl phenylethyl acetal (1.6 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), acetaldehyde ethyl phenylethyl 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), acetaldehyde ethyl phenylethyl acetal does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). 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 neither acetaldehyde ethyl phenylethyl acetal or phenylacetaldehyde dimethyl acetal are sensitizers (RFIM, 1980a; RFIM, 1982b; RFIM, 1982a). In a human repeated insult patch test and a maximization test acetaldehyde ethyl phenylethyl acetal was found to be negative up to 5% or 3450 μg/cm^2 (RIFM, 1964; RIFM, 1975a). Similarly, in a confirmatory human repeated insult patch test (HRIPT) with 1380μg/cm^2 of the read across material phenylacetaldehyde dimethyl acetal in 95% ethanol, no reactions indicative of sensitization were observed in any of the 39 volunteers (RIFM, 1965). Additionally, in a human maximization test, no sensitization reactions were observed when 2% or 1380μg/cm^2 of phenylacetaldehyde dimethyl acetal in petrolatum was used for induction and challenge (RIFM, 1971a). Based on the weight of evidence from structural analysis, animal and human studies and read across, acetaldehyde ethyl phenylethyl acetal does not present a concern for skin sensitization.

Additional References: RIFM, 1975b; RIFM, 1976c; RIFM, 1971b; Klecak, 1979; Klecak, 1985.

Literature Search and Risk Assessment Completed on: 1/18/17

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis spectra and available *in vivo* data, acetaldehyde ethyl phenylethyl acetal would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. The available UV/Vis absorption spectra indicates 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). An *in vivo* phototoxicity study was conducted in rabbits treated with 10% acetaldehyde ethyl phenylethyl acetal in ethanol did not result in phototoxic reactions (RFIM, 1981a). A phototoxicity/photoallergenicity study was conducted in guinea pigs with topical induction using 50% acetaldehyde ethyl phenylethyl acetal in ethanol and challenge with 25% acetaldehyde ethyl phenylethyl acetal in ethanol. There were no phototoxic or photoallergenic reactions (RFIM, 1980b). Based on lack of absorbance and *in vivo* study data, acetaldehyde ethyl phenylethyl acetal does not present a concern for phototoxicity or photoallergenicity.

Additional References: None

Literature Search and Risk Assessment Completed on: 04/07/17

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, acetaldehyde ethyl phenylethyl 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 acetaldehyde ethyl phenylethyl acetal. Based on the Creme RIFM model, the inhalation exposure is 0.025 mg/day. This exposure is 56 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 acetaldehyde ethyl phenylethyl 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, which is considered proprietary information, 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, acetaldehyde ethyl phenylethyl acetal 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 acetaldehyde ethyl phenylethyl acetal as possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

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

10.2.3. Biodegradation

RFIM, 1995: Biodegradation was evaluated by the sealed vessel test according to the OECD 301B method. Filtered activated sludge and 10 mg/l of acetaldehyde ethyl phenylethyl acetal was incubated for 28 days. The rate of degradation after 28 days was 44.3%.

RFIM, 2002a: The biodegradability of acetaldehyde ethyl phenylethyl acetal was evaluated by the Manometric Respirometry Test according to OECD 301F guidelines. Acetaldehyde ethyl phenylethyl acetal (100 mg/l) was added to flasks containing mineral salts medium inoculated with activated sludge. The incubation was conducted for 28 days. The biodegradation rate was 34% at the end of the 10-day window and was 40% after 28 days.

RFIM, 2002b: The inherent biodegradability of the test material was determined by the Respirometric Method according to the OECD 302C method. Acetaldehyde ethyl phenylethyl acetal (30 mg/l) was added to flasks containing mineral salts medium inoculated with activated sludge. The incubation was conducted for 28 days. The biodegradation rate was 59.1% after 28 days.

RFIM, 2011: The ready biodegradability of the test material was evaluated using a Manometric Respirometry Test according to the OECD 301F method. Under the conditions of the study, biodegradation of 48% was observed after 61 days.

Ecotoxicity: No data available.

Other available data: Acetaldehyde ethyl phenylethyl acetal has been pre-registered for REACH with no additional data at this time.

10.2.4. 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)**	19.38 mg/l			1,000,000	0.01938 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	24.17 mg/l	14.93 mg/l	15.76 mg/l	10,000	1.493 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	3.3	3.3
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
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 1.493 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 https://doi.org/10.1016/j.fct.2017.09.040.

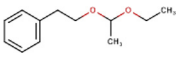
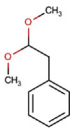
Appendix

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

(*continued*)

	Target material	Read across material
J_{max} (mg/cm^2/h, SAM)	60.202	151.627
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	9.55E-006	5.42E-006
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)	See supplemental data 1	See Supplemental data 2
Rat liver S9 metabolism simulator		

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

Summary

There are insufficient toxicity data on acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7). Hence, *in silico* evaluation was conducted to determine a read across analog for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, analog phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) was identified as a read across material with data for the skin sensitization endpoint.

Conclusion/Rationale

- Phenylacetaldehyde dimethyl acetal (CAS # 101-48-4) could be used as a read across analog for the target material acetaldehyde ethyl phenylethyl acetal (CAS # 2556-10-7) for the skin senzitization toxicity endpoint.
  - o The target substance and the read across analog are structurally similar and belong to the structural class of acetals.
  - o The target substance and the read across analog share an acetal fragment and an alkylphenyl fragment.
  - o The key difference between the target substance and the read across analog is that they have different chain lengths on the acetal substituents. The differences in structure between the target substance and the read across analog do not raise additional structural alerts. Therefore, the structural differences are not relevant from a toxicological endpoint perspective.
  - o 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.
  - 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 senzitization endpoint.
  - o 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 the same. When there is adequate data available, this prediction can be overridden.
  - o The target substance and the read across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for the skin senzitization 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.

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
Q5 Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6 Benzene derivative with certain substituents? No
Q7 Heterocyclic? No
Q16 Common terpene? (see Cramer et al., 1978 for detailed explanation) No
Q17 Readily hydrolyzed to a common terpene? No
Q19 Open chain? Yes
Q20 Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? No
Q23 Aromatic? No
Q27 Rings with substituents? Yes
Q28 More than one aromatic ring? No
Q30 Aromatic ring with complex substituents? No
Q31 Is the substance an acyclic acetal or ester of substances defined in Q30? No
Q18 One of the list? (see Cramer et al., 1978 for detailed explanation on list of categories) No. Class Low (Class I)

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