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Short communication

RIFM fragrance ingredient safety assessment, anisyl phenylacetate, CAS Registry Number 102-17-0

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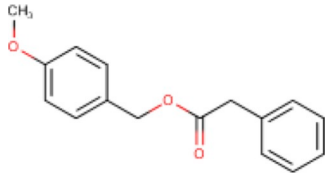

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Abbreviation/Definition List:

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, 2017; Safford et al., 2015a, 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
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/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 as 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 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., 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 with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Anisyl phenylacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that anisyl phenylacetate is not genotoxic. The skin sensitization endpoint was completed using the DST for reactive materials (64 μg/cm^2); exposure is below the DST. Data from read-across analog benzyl benzoate (CAS # 120-51-4) provided an MOE > 100 for the developmental toxicity endpoint. Data from read-across analog phenethyl phenylacetate (CAS # 102-20-5) provided an MOE > 100 for the repeated dose toxicity endpoint. The fertility and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to anisyl phenylacetate is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; anisyl phenylacetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, anisyl phenylacetate 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, 2017a; RIFM, 2017b)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day. (Hagan et al., 1967)
Reproductive Toxicity: Developmental toxicity NOAEL = 7.7 mg/kg/day. No NOAEL available for reproductive toxicity. Exposure is below the TTC. (Morita et al., 1980)
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 2.66 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 166 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 8.162 mg/L (RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

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Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 8.162 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.008162 μg/L (RIFM Framework; Salvito et al., 2002)

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level

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1. Identification

1 **Chemical Name:** Anisyl phenylacetate
2 **CAS Registry Number:** 102-17-0
3 **Synonyms:** Anisyl α-toluate; Benzeneacetic acid, (4-methoxyphenyl)methyl ester; p-Methoxybenzyl phenylacetate; Phenylacetic acid p-methoxybenzyl ester; 4-Methoxybenzyl phenylacetate; Anisyl phenylacetate
4 **Molecular Formula:** $C_{16}H_{16}O_3$
5 **Molecular Weight:** 256.3
6 **RIFM Number:** 947
7 **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 355.29 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA Database)
3. **Log K_{ow}:** 3.87 (EPI Suite)
4. **Melting Point**: 110.32 °C (EPI Suite)
5. **Water Solubility:** 10.82 mg/L (EPI Suite)
6. **Specific Gravity:** 1.12200 to 1.13000 @ 25 °C*
7. **Vapor Pressure:** 0.00000305 mm Hg @ 20 °C (EPI Suite v4.0), 6.38e-006 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor 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 very faint balsamic-rosy odor of great tenacity

*http://www.thegoodscentscompany.com/data/rw1022411.html#tophyp, retrieved 1/9/2018.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0092% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0000005 mg/kg/day or 0.000032 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00025 mg/kg/day (RIFM, 2016)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 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., 2015a; Safford et al., 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	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. **Analogs** Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Phenethyl phenylacetate (CAS # 102-20-5)
   c. **Reproductive Toxicity:** Benzyl benzoate (CAS # 120-51-4)
   d. **Skin Sensitization:** None
   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.

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

Anisyl phenylacetate 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 containing information on published volatile compounds that 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 2010, no dossier available as of 09/10/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, anisyl phenylacetate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Anisyl phenylacetate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects on the target material.

The mutagenic activity of anisyl phenylacetate 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 *Escherichia coli* strain WP2uvrA were treated with anisyl phenylacetate in dimethyl sulfoxide (DMSO) 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 rat liver S9 (RIFM, 2017a). Under the conditions of the study, anisyl phenylacetate was not mutagenic in the Ames test.

The clastogenic activity of anisyl phenylacetate 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 anisyl phenylacetate in DMSO at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h. Micronuclei analysis was conducted up to doses producing appropriate cytotoxicity (up to 819 μg/mL) in all the test conditions. Anisyl phenylacetate did not induce binucleated cells with micronuclei when tested up to the lowest precipitating concentration in either non-activated or S9-activated test systems (RIFM, 2017b). Under the conditions of the study, anisyl phenylacetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, anisyl phenylacetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/01/18.

10.1.2. Repeated dose toxicity

The margin of exposure for anisyl phenylacetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on anisyl phenylacetate. Read-across material phenethyl phenylacetate (CAS # 102-20-5; see Section 5) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. In a dietary 17-week chronic toxicity study, groups of 10 rats/sex/dose were administered 0, 1000, 2500, or 10000 ppm phenethyl phenylacetate (equivalent to 0, 50, 125, or 500 mg/kg/day) in the diet for 17 weeks. No test material related alterations were observed among the treated animals. The NOAEL was considered to be 10000 ppm or 500 mg/kg/day, the highest dose tested (as per the conversion factor for rats, available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives) (Hagan et al., 1967).

Therefore, the anisyl phenylacetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the phenethyl phenylacetate NOAEL in mg/kg/day by the total systemic exposure to anisyl phenylacetate, 500/0.00025 or 2000000. In addition, the total systemic exposure to anisyl phenylacetate (0.25 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) 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: 12/12/17.

10.1.3. Reproductive toxicity

The margin of exposure for anisyl phenylacetate is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient fertility data on anisyl phenylacetate or on any read-across materials. The total systemic exposure to anisyl phenylacetate is below the TTC for the fertility endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on anisyl phenylacetate. Read-across material, benzyl benzoate (CAS # 120-51-4; see Section 5) has sufficient developmental toxicity data. Groups of 21 pregnant Wistar rats were administered diets supplemented with 0.04% or 1% test material benzyl benzoate. Of the 21 females per group, 14 animals were terminated at day 20 and 7 were retained for a 21-day postpartum phase. For the low-dose group (0.04%), the mean total diet consumption was 153.4 mg/rat, equivalent to 7.7 mg/kg/day benzyl benzoate, and for the high-dose group (1%), the mean total consumption was 3886.7 mg/rat, equivalent to 194.3 mg/kg/day. No test material related maternal effects were reported. Fetal abnormalities reported included mandibular defects and the absence of a tongue or a cleft palate in 1 high-dose fetus, but there was no significant difference in incidence when compared to controls. No effects were apparent in the low-dose treatment group. The visceral observations revealed bilateral heterotaxia in 1 high-dose fetus, but there was no significance when compared to controls. Other abnormalities reported included dilation of the renal pelvis (seen in 1 fetus in the low-dose group), dilation of the renal pelvis (2 fetuses), and bisection of the apex (1 fetus) observed in the high-dose group. During the postpartum phase, the fetus bodyweight gains were decreased by day 14 and 21 among the treated dams. However, the effect was not dose-dependent. Overall, even with reports of minor abnormalities among treatment groups but with no significant differences when compared to controls, the study concluded that benzyl benzoate was not teratogenic. The most conservative NOAEL of 0.04% or 7.7 mg/kg/day was considered for the developmental toxicity endpoint, based on alterations reported during the prepartum phase of the study (Morita et al., 1980).

Therefore, the anisyl phenylacetate MOE for the developmental toxicity endpoint can be calculated by dividing the benzyl benzoate NOAEL in mg/kg/day by the total systemic exposure to anisyl phenylacetate, 7.7/0.00025 or 30800. In addition, the total systemic exposure to anisyl phenylacetate (0.25 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint for a Cramer Class I material at the current level of use.

There are insufficient fertility data on anisyl phenylacetate or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to anisyl phenylacetate (0.25 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature **Search and Risk Assessment Completed On:** 12/12/17.

10.1.4. Skin sensitization

Based on the existing data and the application of DST, anisyl phenylacetate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v4.1). No predictive skin sensitization studies are available for anisyl phenylacetate. However, in a human maximization test, no skin sensitization reactions were observed with 12% anisyl phenylacetate (RIFM, 1977).

Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford et al., 2011; Safford et al., 2015b; Roberts et al., 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for anisyl phenylacetate that present no appreciable risk for skin sensitization based on the non-reactive DST. These concentrations are not limits; they represent maximum acceptable concentrations based on the DST approach.

Additional **References:** None.

Literature **Search and Risk Assessment Completed On:** 03/13/18.

Table 1
Maximum acceptable concentrations for anisyl phenylacetate that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.005%	0.000%
2	Products applied to the axillae	0.001%	0.000%
3	Products applied to the face using fingertips	0.029%	0.000%
4	Fine fragrance products	0.027%	0.009%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.007%	0.001%
6	Products with oral and lip exposure	0.016%	0.000%
7	Products applied to the hair with some hand contact	0.056%	0.000%[b]
8	Products with significant ano-genital exposure	0.003%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	0.009%
10	Household care products with mostly hand contact	0.192%	0.000%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.107%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.000%

Note: [a]For a description of the categories, refer to the IFRA/RIFM Information Booklet. [b]Negligible exposure (< 0.001%). [c]Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, anisyl phenylacetate 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 anisyl phenylacetate in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, anisyl phenylacetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for anisyl phenylacetate were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, $1000\ L\ mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/06/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for anisyl phenylacetate 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 anisyl phenylacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.000032 mg/day. This exposure is 43750 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: 01/27/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of anisyl phenylacetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, anisyl phenylacetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 did not identify anisyl phenylacetate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current VoU (IFRA, 20152015), anisyl phenylacetate does not present a risk to the aquatic compartment in the screening-

level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.3. Other available data

Anisyl phenylacetate 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) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>8.162</u>			1000000	0.008162	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.87	3.87
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 class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.008162 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 12/12/17.

11. Literature Search*

- RIFM Database: Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHA: http://echa.europa.eu/
- NTP: https://ntp.niehs.nih.gov/
- 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://webnet.oecd.org/hpv/ui/Default.aspx
- EPA ACToR: https://actor.epa.gov/actor/home.xhtml
- US EPA HPVIS: https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/06/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110626.

Appendix

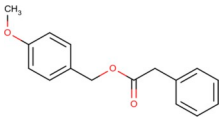
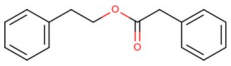
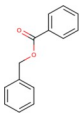
Read-across Justification

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). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by 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 analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).

- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

	Target Material	Read-across Material	
Principal Name	Anisyl phenylacetate	Phenethyl phenylacetate	Benzyl benzoate
CAS No.	102-17-0	102-20-5	120-51-4
Structure			
Similarity (Tanimoto Score)		0.64	0.608
Read-across Endpoint		• Repeated dose toxicity	• Reproductive toxicity
Molecular Formula	$C_{16}H_{16}O_3$	$C_{16}H_{16}O_2$	$C_{14}H_{12}O_2$
Molecular Weight	256.30	240.30	212.25
Melting Point (°C, EPI Suite)	110.32	89.40	70.75
Boiling Point (°C, EPI Suite)	355.29	343.16	317.89
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.000851	0.0248	0.0741
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.87	4.28	3.97
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	10.82	5.921	15.39
J_{max} (μg/cm^2/h, SAM)	2.673	4.5	13.221
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	6.85E-003	1.54E-001	2.84E-001
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Reproductive and Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, without OH or NH2		• Non-binder, without OH or NH2
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)		• Non-toxicant (low reliability)
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on anisyl phenylacetate (CAS # 102-17-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, phenethyl phenylacetate (CAS # 102-20-5) and benzyl benzoate (CAS # 120-51-4) were identified as read-across materials with sufficient data for toxicological evaluation.

12. Conclusions

- Phenethyl phenylacetate (CAS # 102-20-5) was used as a read-across analog for the target material anisyl phenylacetate (CAS # 102-17-0) for the repeated dose toxicity endpoint.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of aromatic esters.
  - ○ The target substance and the read-across analog share aromatic acid and alcohol portions.
  - ○ The key difference between the target substance and the read-across analog is that the target substance has an additional p-methoxy substituent and an additional methylene in the alcohol component of the ester. These structural differences are toxicologically insignificant.
  - ○ Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these aryl alcohol esters of aryl acids. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - ○ 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 endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Benzyl benzoate (CAS # 120-51-4) was used as a read-across analog for the target material anisyl phenylacetate (CAS # 102-17-0) for the reproductive toxicity endpoint.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of aromatic esters.
  - ○ The target substance and the read-across analog share aromatic acid and alcohol portions.
  - ○ The key difference between the target substance and the read-across analog is that the target substance is a p-methoxy benzyl alcohol ester of phenylacetate, whereas the read-across analog is a benzyl alcohol ester of benzoic acid These structural differences are toxicologically insignificant.

- Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these aromatic acid and alcohol esters. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target substance corresponds to skin absorption $\leq 40\%$ and J_{max} for the read-across analog corresponds to skin absorption $\leq 80\%$. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
- According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- 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 endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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