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Short Review

RIFM fragrance ingredient safety assessment, hexyl phenylacetate, CAS Registry Number 5421-17-0

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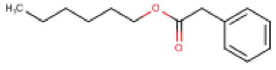

Version: 011819. This version replaces any previous versions.
Name: Hexyl phenylacetate
CAS Registry Number: 5421-17-0

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

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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; Safford 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
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.

Hexyl phenylacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog methyl phenylacetate (CAS # 101-41-7) show that hexyl phenylacetate is not expected to be genotoxic and provide a calculated MOE > 100 for the repeated dose toxicity endpoint. Data on read-across material ethyl phenylacetate (CAS # 101-97-3) provide a calculated MOE > 100 for the reproductive toxicity endpoint. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to hexyl phenylacetate is below the TTC (1.4 mg/day). Data from read-across analog methyl benzoate (CAS # 93-58-3) show that there are no safety concerns for hexyl phenylacetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; hexyl phenylacetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; hexyl 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 expected to be genotoxic.	(RIFM, 2001; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 66.66 mg/kg/day.	ECHA REACH Dossier: Methyl Phenylacetate; ECHA (2016b)
Reproductive Toxicity: NOAEL = 200 mg/kg/day.	ECHA REACH Dossier: Ethyl Phenylacetate; ECHA (2016a)
Skin Sensitization: Not a concern for skin sensitization at the current, declared levels of use.	ECHA REACH Dossier: Methyl Benzoate; ECHA (2013)
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: 3.1 (BIOWIN 3)	(EPI Suite v.4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 457 L/kg	(EPI Suite v.4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 1.98 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 1.98 mg/L (RIFM Framework; Salvito et al., 2002)	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00198 μg/L	

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

1. Identification

1. **Chemical Name:** Hexyl phenylacetate
2. **CAS Registry Number:** 5421-17-0
3. **Synonyms:** Benzeneacetic acid, hexyl ester; Hexyl α-toluate; Hexyl phenylacetate
4. **Molecular Formula:** $C_{14}H_{20}O_2$
5. **Molecular Weight:** 220.31
6. **RIFM Number:** 1306
7. **Stereochemistry:** No stereocenter and no stereoisomer possible.

2. Physical data

1. **Boiling Point**: 300.23 °C (EPI Suite)
2. **Flash Point**: > 200 °F; CC (FMA Database)
3. **Log K_{OW}**: 4.54 (EPI Suite)
4. **Melting Point**: 52.39 °C (EPI Suite)
5. **Water Solubility:** 4.582 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.01 mm Hg 20 °C (FMA Database), 0.00108 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Arctander, Volume I, 1969: Colorless oily liquid. Sweet-green, fruity-winey odor, overall rather weak, but tenacious and with undertones that may vary from rosy to musky, according to the origin of the sample.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric ton per year (IFRA , 2015)
2. **95**th **Percentile Concentration in Toothpaste:** 0.001% (RIFM, 2017)

No reported use in hydroalcoholics

3. **Inhalation Exposure*** < 0.0001 mg/kg/day or < 0.0001 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0000063 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015; 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., 2015; 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:** Methyl phenylacetate (CAS # 101-41-7)
   b. **Repeated Dose Toxicity:** Methyl phenylacetate (CAS # 101-41-7)
   c. **Reproductive Toxicity:** Ethyl phenylacetate (CAS # 101-97-3)
   d. **Skin Sensitization:** Methyl benzoate (CAS # 93-58-3)
   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.

6.1. Additional References

None.

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

Hexyl phenylacetate is not reported to occur foods 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 01/17/19.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, hexyl phenylacetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of hexyl phenylacetate; however, read-across can be made to methyl phenylacetate (CAS # 101-41-7; see Section 5). The mutagenic activity of methyl 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 TA102 were treated with hexyl 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 concentration in the presence or absence of S9 (RIFM, 2001). Under the conditions of the study, methyl phenylacetate was not mutagenic in the Ames test, and this can be extended to hexyl phenylacetate.

The clastogenic activity of methyl 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 methyl phenylacetate in DMSO at concentrations up to 1500 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Methyl phenylacetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels/the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, methyl phenylacetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to hexyl phenylacetate.

Based on the available data, methyl phenylacetate does not present a concern for genotoxic potential, and this can be extended to hexyl phenylacetate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/02/19.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) 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 hexyl phenylacetate. Read-across material methyl phenylacetate (CAS # 101-41-7; see Section 5) has sufficient repeated dose toxicity data. In an OECD 422 and GLP-compliant study, 12 SD rats/sex/dose were administered methyl phenylacetate by oral gavage at doses of 0 (vehicle: corn oil), 50, 200, and 800 mg/kg/day, for 2 weeks prior to mating and through the day before euthanasia in males (at least 50 days) and through lactation day 13 in females. Recovery groups of 6 animals/sex/dose were maintained for 2 weeks for the 0 and 800 mg/kg/day doses. No mortality was reported throughout the study at any dose level. However, statistically significant decreases in bodyweight gain (76% and 69% of control, for males and females, respectively) were reported in the high-dose group during study days 1–50. In addition, treatment-related statistically significant changes in hematological parameters were reported at the highest dose. These changes included a 20% decrease of platelet counts in both the sexes, a 17% reduction of absolute and relative reticulocyte counts in females, and a 40–50% decrease of absolute and relative eosinophil counts in males. Furthermore, high-dose treatment resulted in significant increases of absolute (females only) and relative liver weights (both sexes), decreases in absolute and relative adrenal gland weights with decreased absolute weight of the prostate gland in males, and increases in relative and absolute heart weight in females. Since these changes were reversed following the recovery period and were not accompanied by a histopathological change, they were not considered adverse. Therefore, based on the decrease in bodyweight gain combined with hematological alterations and organ weight changes at the highest dose, the NOAEL was considered to be 200 mg/kg/day for repeated dose toxicity (https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/16699/1, ECHA, 2016b).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 study. The safety factor has been approved by The Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 200/3 or 66.66 mg/kg/day.

Therefore, the MOE can be calculated by dividing the NOAEL for methyl phenylacetate by the total systemic exposure of hexyl phenylacetate, 66.66/0.0000063 or 10580952.

In addition, the total systemic to hexyl phenylacetate (0.0063 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.

*The Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/04/19.

10.1.3. Reproductive toxicity

The MOE for hexyl phenylacetate is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on hexyl phenylacetate. Read-across material ethyl phenylacetate (CAS # 101-97-3; see Section 5) has sufficient reproductive toxicity data. In an OECD 422 and GLP-compliant study, 12 Sprague Dawley rats/sex/dose were administered ethyl phenylacetate via oral gavage at doses of 0, 50, 200, or 800 mg/kg/day in corn oil. Males were dosed for at least 50 days (2 weeks prior to mating until the day before scheduled necropsy), while females were doses for 2 weeks prior to mating and continued through lactation day (LD) 13. Additional groups of 6 rats/sex/dose were administered control or doses but not mated and assigned to the control and high-dose group to serve as the 14-day treatment-free recovery groups. In addition to systemic toxicity parameters, reproductive toxicity parameters were also assessed. No mortality of the parental generation was reported throughout the study at any dose level. A statistically significant decrease in bodyweight gain (76% and 69% of control, for males and females, respectively) was reported at 800 mg/kg during study days 1–50. Decreased regularity of the estrus cycle (75%) was observed in high-dose dams. At 800 mg/kg/day, statistically significant increases in gestation period and perinatal death and statistically significant decreases in live litter size and viability index were observed. Body weights of male and female pups were statistically significantly decreased on postnatal day (PND) 0 (88% and 83% of control, respectively) and PND 13 (91% and 90% of control, respectively). Thus, the NOAEL for fertility and developmental toxicity was considered to be 200 mg/kg/day, based on decreases in the regularity of the estrus cycle, live litter size, viability index and body weights of F1 pups, and increases in gestation period and perinatal death observed among the high-dose group animals (https://echa.europa.eu/lt/registration-dossier/-/registered-dossier/16453/7/9/1, ECHA, 2016a). **Therefore, the hexyl phenylacetate MOE can be calculated by dividing the ethyl phenylacetate NOAEL by the total systemic exposure to hexyl phenylacetate, 200/0.0000063 or 31746032.**

In addition, the total systemic exposure to hexyl phenylacetate (0.0063 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/18/19.

10.1.4. Skin sensitization

Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3), hexyl phenylacetate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for hexyl phenylacetate. Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3; see Section 5), hexyl phenylacetate is not considered to be a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material methyl benzoate was found to be negative up to the maximum tested concentration of 100%, which resulted in a Stimulation Index (SI) of 2.98 (https://echa.europa.eu/registration-dossier/-/registered-dossier/13833/7/5/2, ECHA, 2013). In guinea pigs, open epicutaneous tests with read-across material methyl benzoate did not present reactions indicative of sensitization (Klecak, 1985; Hausen et al., 1995). In a human maximization test, no skin sensitization reactions were observed with 4% or 2760 μg/cm^2 read-across material methyl benzoate in petrolatum (RIFM, 1970).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material methyl benzoate, hexyl phenylacetate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: Hausen et al., 1995.

Literature Search and Risk Assessment Completed On: 12/06/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra, hexyl 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 hexyl phenylacetate in experimental models. UV absorption spectra indicate no absorption between 290 and 500 nm. As such, it is not a concern for phototoxicity or photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, hexyl phenylacetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available spectra indicate no absorbance in the range of 290–500 nm. As the material does not absorb in the range of interest, it is not a concern for phototoxicity or photoallergenicity (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/20/18.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to lack of appropriate data. The exposure level for hexyl 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 hexyl phenylacetate. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 14000 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: 12/12/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of hexyl 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, hexyl 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 (US EPA, 2012a) did not identify hexyl 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).

10.2.1.1. Risk assessment. Based on the current Volume of Use (2015), hexyl phenylacetate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Biodegradation. No data available.

10.2.1.3. Ecotoxicity. No data available.

10.2.1.4. Other available data. Hexyl phenylacetate has been pre-registered for REACH with no additional data at this time.

10.2.2. 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*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.98			1000000	0.00198	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.5	4.5
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 0.00198 μg/L. The revised PEC/PNECs for EU and NA: not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 12/12/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/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:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **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 05/31/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.111021.

Appendix

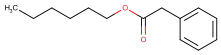
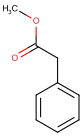
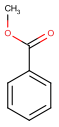
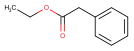
Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as 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 Chemical Agency read-across assessment framework (ECHA, 2016c).

- 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 material 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 v4.2 (OECD, 2018).

- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Hexyl phenylacetate	Methyl phenylacetate	Methyl benzoate	Ethyl phenylacetate
CAS No.	5421-17-0	101-41-7	93-58-3	101-97-3
Structure				
Similarity (Tanimoto Score)		0.70	0.30	0.78
Read-across Endpoint		• Genotoxicity • Repeated Dose Toxicity	• Skin Sensitization	• Reproductive Toxicity
Molecular Formula	$C_{14}H_{20}O_2$	$C_9H_{10}O_2$	$C_8H_8O_2$	$C_{10}H_{12}O_2$
Molecular Weight	220.31	150.17	136.15	164.20
Melting Point (°C, EPI Suite)	52.39	−0.50	−15	−29.4
Boiling Point (°C, EPI Suite)	300.23	215.57	199	227
Vapor Pressure (Pa @ 25-°C, EPI Suite)	0.144	20.9	5.07E+001	12.2
Log K_{OW}(KOWWIN v1.68 in EPI Suite)	4.54	1.83	2.12	2.28
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	4.582	2072	1344	739.4
J_{max} (μg/cm^2/h, SAM)	0.51	78.18	77.62	44.26
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.91E+000	1.43E+000	3.28E+000	1.90E+000
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	• Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	• Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes		
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (moderate reliability)		
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found		
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found		
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found		
Oncologic Classification	• Not classified	• Not classified		
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized	• Diclofenac (Hepatotoxicity) Alert • Styrene (Renal Toxicity) Alert • Toluene (Renal toxicity) Alert		
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group			• Non-binder, without OH or NH2 group
Developmental Toxicity (-CAESAR v2.1.6)	• Non-toxicant (low reliability)			• Non-toxicant (low reliability)
Skin Sensitization				
Protein Binding (OASIS v-1.1)	• No alert found		• No alert found	
Protein Binding (OECD)	• No alert found		• No alert found	
Protein Binding Potency	• Not possible to classify according to these rules (GSH)		• Slightly reactive (GSH)|Slightly reactive (GSH) ≫ Reaction at sp3 carbon atom (SN2)	

Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found		• No alert found	
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3	• See Supplemental Data 4

Summary

There are insufficient toxicity data on hexyl phenylacetate (CAS # 5421-17-0). 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, methyl phenylacetate (CAS # 101-41-7), methyl benzoate (CAS # 93-58-3), and ethyl phenylacetate (CAS # 101-97-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Methyl phenylacetate (CAS # 101-41-7) was used as a read-across analog for the target material hexyl phenylacetate (CAS # 5421-17-0) for the genotoxicity and repeated dose toxicity.
  - o The target material and the read-across analog are structurally similar and belong to a class of aromatic esters.
  - o The target material and the read-across analog share a phenylacetate group.
  - o The key difference between the target material and the read-across analog is the alcohol moiety of the ester (hexanol in the target material and methanol in the read-across analog). This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both target and read-across materials show DNA Binding (OASIS v1.4) P450 Michael addition alerts due to the aromatic benzyl group. Data are consistent with *in silico* alerts.
  - o The read-across analog displays several alerts for repeated dose toxicity that are not found in the target material. Those alerts are due to structural similarity of the read-across analog with compounds that display repeated dose toxicity (approximately 50% Dice similarity score). According to these predictions, the read-across analog is expected to be more reactive compared to the target material. Data supersedes predictions in this case.
  - o The target material 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.
- Methyl benzoate (CAS # 93-58-3) was used as a read-across analog for the target material hexyl phenylacetate (CAS # 5421-17-0) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of aromatic esters.
  - o The target material and the read-across analog share aryl acyl ester structures.
  - o The key difference between the target material and the read-across analog is the alcohol moiety of the ester (hexanol in the target material and methanol in the read-across analog). The target material is a phenylacetate while the read-across analog is a benzoate. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Data are consistent with *in silico* alerts.
  - o The read-across analog displays an alert for protein binding potency that is not found in the target material. This alert is due to the benzoate group, which has 1 less branched carbon than the phenylacetate moiety in the target material. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. Data superseded predictions in this case.
  - o The target material 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.
- Ethyl phenylacetate (CAS # 101-97-3) was used as a read-across analog for the target material hexyl phenylacetate (CAS # 5421-17-0) for the reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of aromatic esters.
  - o The target material and the read-across analog share a phenylacetate group.
  - o The key difference between the target material and the read-across analog is the alcohol of the ester (hexanol in the target material and ethanol in the read-across analog). This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that

affect the Tanimoto score are toxicologically insignificant.

- o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o The target material 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.

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