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Short Review

RIFM fragrance ingredient safety assessment, methyl phenylacetate, CAS Registry Number 101-41-7

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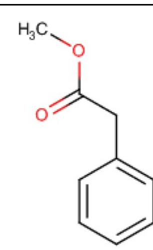
Version: 050418. This version replaces any previous versions.
Name: Methyl phenylacetate **CAS Registry Number:** 101-41-7



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., 2015, 2017) compared to a deterministic aggregate approach

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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 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 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 use of this material under current conditions is supported by existing information.

Methyl phenylacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data show that methyl phenylacetate is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material, and the exposure to methyl phenylacetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data on methyl phenylacetate and the read-across analog methyl benzoate (CAS# 93-58-3) show that methyl phenylacetate does not present a safety concern at the current, declared levels of use for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; methyl phenylacetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, methyl 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, 2001a; RIFM, 2015a)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: No safety concerns under the current, declared levels of use.	(ECHA REACH Dossier: methyl benzoate, accessed 6/14/17)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 75% (OECD 301D)	(RIFM, 2001b)
Bioaccumulation: Screening-level: 7.4 L/kg	(EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 247.3 mg/L (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 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 247.3 mg/L (Salvito et al., 2002)
RIFM PNEC is: 0.2473 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe; Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Methyl phenylacetate
2. **CAS Registry Number:** 101-41-7
3. **Synonyms:** Benzeneacetic acid, methyl ester; Methyl α-toluate; ﾌｴﾆﾙｱﾙｶﾝ酸(C = 2 ~ 5)ｱﾙｷﾙ(C = 1 ~ 8); Methylphenylacetat; Methyl phenylacetate
4. **Molecular Formula:** $C_9H_{10}O_2$
5. **Molecular Weight:** 150.18
6. **RIFM Number:** 511

2. Physical data

1. **Boiling Point:** 220 °C (FMA Database), 215.57 °C (EPI Suite), 218.4 °C at 1013 hPa (RIFM, 2015b)
2. **Flash Point:** 97 °C (GHS), 99.5 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015c)
3. **Log K_{OW}:** 2.08 (EPI Suite), 1.91 at 21.9 °C (RIFM, 2016a)
4. **Melting Point:** 0.5 °C (EPI Suite), −23.7 °C at 1001 hPa (RIFM, 2015b)
5. **Water Solubility:** 2072 mg/L (EPI Suite)
6. **Specific Gravity:** 1.063–1.069 (FMA Database), 1.061–0.067 (FMA Database)
7. **Vapor Pressure:** 0.104 mm Hg @ 20 °C (EPI Suite), 0.1 mm Hg 20C (FMA Database), 0.157 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})

Appearance/Organoleptic: A colorless to very pale yellow liquid with an intense odor suggestive of honey and jasmine (Arctander, 1969).

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.011% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00014 mg/kg/day or 0.010 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0031 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 IV. 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. **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe; Not applicable; cleared at the screening-level 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:** None
   c. **Reproductive Toxicity:** None
   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

Not considered for this risk assessment.

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

Methyl phenylacetate is reported to occur in nature in the following*:

Beef
Beli, bael (*Aegle marmelos* Correa)
Capsicum species
Ceriman, pinanona (*Monstera deliciosa* Liebm.)
Cocoa category
Coffee
Grape brandy
Honey
Hop (*Humulus lupulus*)
Mountain papaya (*C. candamarcensis, C. pubescens*)
Passion fruit (*Passiflora* species)
Peanut (*Arachis hypogaea* L.)
Pepper (*Piper nigrum* L.)
Pineapple (*Ananas comosus*)
Rooibos tea (*Aspalathus linearis*)
Starfruit (*Averrhoa carambola* L.)
Tea
Vanilla
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 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

Available, accessed 6/15/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Methyl phenylacetate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). The mutagenic activity of methyl phenylacetate (CAS # 101-41-7) 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 TA97a, TA98, TA100, TA1535, and TA102 were treated with methyl 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 S9 (RIFM, 2001a). Under the conditions of the study, methyl phenylacetate was not mutagenic in the Ames test.

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 and 24 h. Methyl phenylacetate did not induce binucleated cells with micronuclei when tested up to the maximum allowed concentration in either non-activated or S9-activated test systems (RIFM, 2015a). Under the conditions of the study, methyl phenylacetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/19/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on methyl phenylacetate or any read-across materials. The total systemic exposure to methyl phenylacetate 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 methyl phenylacetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to methyl phenylacetate (3.1 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: 06/05/2017.

10.1.3. Reproductive toxicity

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

10.1.3.1. Risk assessment. There are no reproductive toxicity data on methyl phenylacetate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to methyl phenylacetate (3.1 μg/kg/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: 06/05/2017.

10.1.4. Skin sensitization

Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3), methyl phenylacetate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for methyl phenylacetate. Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3; see Section V), methyl phenylacetate does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structures of these materials indicate that they could possibly react with skin proteins with little to no reaction under physiological conditions. In guinea pigs, an open epicutaneous test did not present reactions indicative of sensitization in methyl phenylacetate (Klecak, 1985). Read-across material methyl benzoate does not present a concern for skin sensitization. In a murine local lymph node assay, 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 (ECHA REACH Dossier: Methyl benzoate, accessed 6/14/17). In guinea pigs, an open epicutaneous test and Freund's complete adjuvant test 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 8% or 5520 μg/cm^2 methyl phenylacetate in petrolatum (RIFM, 1974). In a human maximization test of the read-across material methyl benzoate, no skin sensitization reactions were observed with 4% or 2760 μg/cm^2 in petrolatum (RIFM, 1970). Based on weight of evidence from structural analysis and animal and human studies, methyl phenylacetate does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 6/15/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, methyl 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 methyl phenylacetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, methyl phenylacetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD test guideline 101) were obtained. The spectra indicate no significant 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} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/25/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for methyl 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 methyl phenylacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.010 mg/day. This exposure is 140 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: 5/26/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of methyl 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, methyl phenylacetate was identified as a fragrance material with the potential no 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 did not identify methyl 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 v4.1). 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 Volume of Use (2015), methyl phenylacetate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2001b: The ready biodegradability of the test material was evaluated according to the OECD 301D method. After 28 days, biodegradation of 75% was observed.

10.2.2.2. Ecotoxicity. RIFM, 2001c: A *Daphnia magna* immobilization test was conducted according to the OECD 202I method under static conditions. The 48-h EC50 was reported to be 117 mg/L.

RIFM, 2016b: An algae growth inhibition test was conducted according to the OECD 201 method. Under the conditions of this study, the EC50 values for inhibition of growth rate (ErC50) and yield (EyC50) after 72 h were 61.9 mg/L and 48.5 mg/L, respectively.

10.2.2.3. Other available data. Methyl phenylacetate has been registered under REACH, and the following additional data is available:

A fish (*Danio rerio*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 was reported to be 16.14 mg/L.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	247.3			1,000,000	0.2473	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.9	1.9
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	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 0.2473 μg/L. The revised PEC/PNECs for EU and NA are < 1: not applicable, cleared at the screening-level and therefore the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 6/15/17.

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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

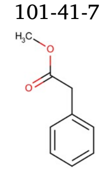
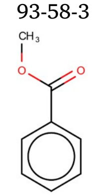
Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2018.10.007.

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 Chemical 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 (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, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- 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, 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	Methyl phenylacetate	Methyl benzoate
CAS No.	101-41-7	93-58-3
Structure		
Similarity (Tanimoto score)		0.833
Read-across endpoint		• Skin Sensitization

Molecular Formula	$C_9H_{10}O_2$	$C_8H_8O_2$
Molecular Weight	150.18	136.15
Melting Point (°C, EPI Suite)	−0.50	−11.87
Boiling Point (°C, EPI Suite)	215.57	195.93
Vapor Pressure (Pa @ 25°C, EPI Suite)	20.9	5.07E+001
Log Kow (KOWWIN v1.68 in EPI Suite)	1.83	2.12
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2072	2100
J_{max} (mg/cm^2/h, SAM)	78.176	77.618
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.43E+000	3.52E+000
Skin Sensitization		
Protein binding by OASIS v1.1	• No alert found	• Acylation
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	• Not possible to classify	• No alert found
Skin Sensitization reactivity domains (ToxTree v2.6.13)	• No alert found	• No alert found
Metabolism		
OECD QSAR Toolbox (3.4)	See Supplemental Data 1	See Supplemental Data 2
Rat liver S9 metabolism simulator and structural alerts for metabolites		

Summary

There are insufficient toxicity data on the target material methyl phenylacetate (CAS # 101-41-7). 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, methyl benzoate (CAS # 93-58-3) was identified as read-across analog with sufficient data for the skin sensitization endpoint.

Conclusions

- Methyl benzoate (CAS # 93-58-3) was used as a read-across analog for the target material methyl phenylacetate (CAS # 101-41-7) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the structural class of aromatic esters.
  - The target substance and the read-across analog share an aromatic acid portion and a straight chain saturated alcohol portion.
  - The key difference between the target and the read-across analog is that the acid portion on the target substance has a carboxylic acid insulated by 1 carbon from the aromatic moiety while the carboxylic acid in the read-across analog has a carboxylic acid conjugated with the aromatic moiety. The carboxylic acid portion in the read-across analog is a stronger acid (lower pKa) compared to the acid portion in the target substance (higher pKa). This difference between the target substance and the read-across analog makes the read-across analog more reactive compared to the target substance. This structural difference between the target substance and the read-across analog does not affect consideration of the toxicological endpoint.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the tanimoto score do not affect consideration of the toxicological endpoint.
  - 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 QSAR OECD Toolbox (v3.4), structural alerts for the toxicological endpoint are consistent between the target substance and the read-across analog.
  - The read-across analog has a protein binding alert by OASIS. This shows that the read-across analog is more reactive than the target substance. The data described in the skin sensitization section show that the read-across analog does not pose a concern for skin sensitization. Therefore, the alert will be superseded by the available data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural differences between the target material and the read-across analog do not affect consideration of the toxicity endpoint.

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