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Short Review

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

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], J. Muldoon [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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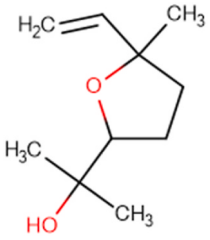

Name: Methyl phenylacetate
CAS Registry Number: 101-41-7

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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
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
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
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

(*continued on next column*)

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(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.

Methyl phenylacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl phenylacetate is not genotoxic. Data on methyl phenylacetate provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across material ethyl phenylacetate (CAS # 101-97-3) show that there are no safety concerns for methyl phenylacetate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; methyl phenylacetate is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to methyl phenylacetate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; methyl phenylacetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2001a; RIFM, 2015a)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	ECHA (2012b)
Reproductive Toxicity: NOAEL = 556 mg/kg/day.	ECHA (2012b)
Skin Sensitization: Not a concern for skin sensitization.	(RIFM, 2016d; RIFM, 2016c)
Photoirritation/Photoallergenicity: Not expected to be a photoirritant or photoallergen.	(UV/Vis Spectra; RIFM Database)

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 v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 247.3 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 247.3 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.2473 μg/L

- **Revised PEC/PNECs (2019 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; ｱﾙｷﾙｶﾝ酸(C = 2~5)ﾌｪﾆﾙ(C = 1~8); Methylphenylacetat; Methyl phenylacetate
4. **Molecular Formula:** $C_9H_{10}O_2$
5. **Molecular Weight:** 150.17 g/mol
6. **RIFM Number:** 511

7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 220 °C (Fragrance Materials Association [FMA]), 215.57 °C (EPI Suite v4.11), 218.4 °C at 1013 hPa (RIFM, 2015b)
2. **Flash Point:** 97 °C (Globally Harmonized System), 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 v4.11)
6. **Specific Gravity:** 1.063–1.069 (FMA), 1.061–0.067 (FMA)
7. **Vapor Pressure:** 0.104 mm Hg at 20 °C (EPI Suite v4.0), 0.1 mm Hg at 20 °C (FMA), 0.157 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless to very pale yellow liquid with an intense odor suggestive of honey and jasmine (Arctander, Volume II, 1969)

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.5)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0075% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0079 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.0011 mg/kg/day (RIFM, 2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015; Safford, 2015; Safford, 2017; Comiskey, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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, 2015; Safford, 2015; Safford, 2017; Comiskey, 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
I	I	I

2. Analogs Selected:

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Ethyl phenylacetate (CAS # 101-97-3)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

Methyl phenylacetate is reported to occur in the following foods by the VCF*.

Beef	Coffee
Beli, Bael (*Aegle marmelos Correa*)	Grape brandy
Capsicum species	Hop (*Humulus lupulus*)
Ceriman, pinanona (*Monstera deliciosa* Liebm.)	Mountain papaya (*C. candamarcensis*, *C. pubescens*)
Chicory (*Cichorium intrybus* L.)	
Cocoa category	

*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. This is a partial list.

9. REACH dossier

Available (ECHA, 2012b); accessed on 10/28/22.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Methyl 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, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

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: 01/27/23.

11.1.2. Repeated dose toxicity

The MOE for methyl phenylacetate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on methyl phenylacetate.

In a GLP- and OECD 422-compliant study, groups of 13 Wistar rats/sex/dose were administered methyl phenylacetate via gavage (vehicle: corn oil) at doses of 0, 308, 556, or 1000 mg/kg/day for 63 days. Additional groups of 5 rats/sex/dose were assigned to the control and high-dose groups and maintained as recovery groups for 14 days after the treatment period. There were no treatment-related adverse effects observed up to the highest dose. Based on no adverse effects seen up to the highest dose, the repeated dose toxicity NOAEL for this study was considered to be 1000 mg/kg/day (ECHA, 2012b).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012a). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the methyl phenylacetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl phenylacetate NOAEL in mg/kg/day by the total systemic exposure to methyl phenylacetate, 333/0.0011 or 302727.

In addition, the total systemic exposure to methyl phenylacetate (1.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*The Expert Panel for Fragrance Safety 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: 12/07/22.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on methyl phenylacetate. In a GLP- and OECD 422-compliant study, groups of 13 Wistar rats/sex/dose were administered methyl phenylacetate via gavage (vehicle: corn oil) at doses of 0, 308, 556, or 1000 mg/kg/day for 63 days. Additional groups of 5 rats/sex/dose were assigned to the control and high-dose group and maintained as recovery groups for 14 days after the treatment period. There were no toxicologically significant adverse effects seen in gestational length. Prolonged diestrous (i.e., more than 3 days with a total estrous cycle period of 6 days or more before the mating period) was observed in females at the mid and high doses. Pregnancy indices for the control, low, mid, and high doses were 92.3%, 84.62%, 84.62%, and 61.54% groups, respectively (significant only at the highest dose). The fertility index was decreased in females at the high dose, which was considered to be treatment-related. This was correlated with reduced pup viability at the high dose. Based on decreased fertility index and decreased pup viability at 1000 mg/kg/day, the fertility and developmental toxicity NOAEL for this study was considered to be 556 mg/kg/day (ECHA, 2012b).

Therefore, the methyl phenylacetate MOE for the reproductive toxicity endpoint can be calculated by dividing the methyl phenylacetate NOAEL in mg/kg/day by the total systemic exposure to methyl phenylacetate, 556/0.0011 or 181818.

In addition, the total systemic exposure to methyl phenylacetate (1.1 μg/kg/day) is below the TTC (30 μg/kg/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: 12/07/22.

11.1.4. Skin sensitization

Based on the existing data on the target material and read-across material ethyl phenylacetate (CAS # 101-97-3), methyl phenylacetate presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for methyl phenylacetate. Therefore, ethyl phenylacetate (CAS # 101-97-3; see Section VI) was used for the risk assessment of methyl phenylacetate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, methyl phenylacetate is not considered a skin sensitizer. Methyl phenylacetate and read-across material ethyl phenylacetate are predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Read-across material ethyl phenylacetate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and human cell line activation test (h-CLAT) (RIFM, 2016d; RIFM, 2016c). Read-across material ethyl phenylacetate was concluded to be a non-sensitizer when these *in vitro* data were evaluated following the 2 out of 3 defined approach in OECD Guideline No. 497 (OECD, 2021a). In guinea pigs, an open epicutaneous test (OET) did not present reactions indicative of sensitization in methyl phenylacetate (Klecak, 1979, 1985). Additionally, an OET in guinea pigs did not present reactions indicative of sensitization with read-across material ethyl phenylacetate (Klecak, 1979, 1985). In a human maximization test, no skin sensitization reactions were observed when methyl phenylacetate was tested at 5520 μg/cm^2 (RIFM, 1974). In a human maximization test, no skin sensitization reactions were observed when read-across material ethyl phenylacetate was tested at 5520 μg/cm^2 (RIFM, 1973).

Based on weight of evidence (WoE) from structural analysis and *in vitro*, animal, and human studies on the read-across material ethyl phenylacetate and the target material, methyl phenylacetate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/16/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, methyl phenylacetate would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for methyl phenylacetate in experimental models. UV/Vis absorption

Table 1
Summary of existing data on ethyl phenylacetate as a read-across for methyl phenylacetate.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL (induction) µg/cm²	WoE NESIL µg/cm²	LLNA Weighted Mean EC3 Value µg/cm²	GPMT	Buehler
No evidence of sensitization[3]	N/A	5520	N/A	N/A	N/A	N/A	N/A
	In vitro Data[2]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative	N/A	Negative		No alert found	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available

[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[2]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[3]Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). ased on the lack of absorbance, methyl phenylacetate does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating or photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/13/23.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for methyl phenylacetate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on methyl phenylacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.0079 mg/day. This exposure is 177.2 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: Johnson et al., 2005.

Literature Search and Risk Assessment Completed On: 01/23/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methyl phenylacetate was performed following the RIFM Environmental Framework (Salvito, 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 VoU 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 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 methyl phenylacetate as possibly being 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, 2017a). 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.

11.2.1.1. Risk assessment. Based on the current VoU (2019), methyl phenylacetate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. 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.

11.2.1.2.2. 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.

11.2.1.2.3. Other available data. Methyl phenylacetate has been registered under REACH, and the following additional data is available (ECHA, 2012b):

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.

11.2.1.3. Risk assessment refinement. Since methyl phenylacetate has passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito, 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 VoU 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 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: 01/18/23.

12. 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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/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 07/31/23.

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

	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			1000000	0.2473	

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

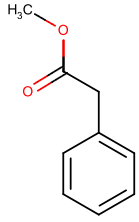
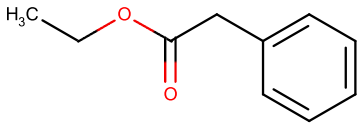
Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.114335.

Appendix

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017b).

- 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 (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 v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

Principal Name	Target Material	Read-across Material
	Methyl phenylacetate	Ethyl phenylacetate
CAS No.	101-41-7	101-97-3
Structure		
Similarity (Tanimoto Score)		0.90
SMILES	COC(=O)Cc1ccccc1	CCOC(=O)Cc1ccccc1
Endpoint		Skin sensitization
Molecular Formula	$C_9H_{10}O_2$	$C_{10}H_{12}O_2$
Molecular Weight (g/mol)	150.177	164.204
Melting Point (°C, EPI Suite)	−0.50	−29.40
Boiling Point (°C, EPI Suite)	216.50	227.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.09E+01	1.22E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.07E+03	7.39E+02
Log K_{OW}	1.83	2.28
J_{max} (μg/cm^2/h, SAM)	34.79	17.82
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.44E+00	1.90E+00
Skin Sensitization		
Protein Binding (OASIS v1.1)	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)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified	No skin sensitization reactivity domain alerts were identified

(*continued on next page*)

(*continued*)

Principal Name	Target Material	Read-across Material
	Methyl phenylacetate	Ethyl phenylacetate
Respiratory Sensitization (OECD QSAR Toolbox v4.5)	No alert found	No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on methyl phenylacetate (CAS # 101-41-7). 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, ethyl phenylacetate (CAS # 101-97-3) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Ethyl phenylacetate (CAS # 101-97-3) was used as a read-across analog for the target material, methyl phenylacetate (CAS # 101-41-7), for the skin sensitization endpoint.
  - o The target material and the read-across analog are phenyl esters with the target having methyl functionalization and the read-across analog having ethyl functionalization.
  - o The key difference between the target material and the read-across analog is the target material is a methyl ester while the read-across analog is an ethyl ester. This structural difference is toxicologically insignificant.
  - o The 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 a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog do not display *in silico* alerts for the skin sensitization endpoint. Data for the read-across analog indicates that it is not a concern for skin sensitization. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are consistent with the data.
  - 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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