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Short Review

RIFM fragrance ingredient safety assessment, α-methylbenzyl propionate, CAS Registry Number 120-45-6

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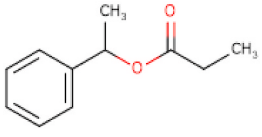
Name: α-Methylbenzyl propionate
CAS Registry Number: 120-45-6



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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)

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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; Safford et al., 2015a; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
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 (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.

α-Methylbenzyl propionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog α-methylbenzyl acetate (CAS # 93-92-5) show that α-methylbenzyl propionate is not expected to be genotoxic. Data from read-across analog α-methylbenzyl acetate (CAS # 93-92-5) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from read-across analog benzyl acetate (CAS # 140-11-4) show that there are no safety concerns for α-methylbenzyl propionate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; α-methylbenzyl propionate is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the analog benzyl acetate (CAS # 140-11-4). The environmental endpoints were evaluated; α-methylbenzyl propionate 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.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2019; RIFM, 2015)

Repeated Dose Toxicity: NOAEL = 150 mg/kg/day. (Gaunt et al., 1974)

Reproductive Toxicity: Developmental toxicity NOAEL = 200 mg/kg/day. Fertility NOAEL = 500 mg/kg/day. (RIFM, 2020a; RIFM, 2020b)

Skin Sensitization: No concern for skin sensitization under the current, declared levels of use. (RIFM, 1985b; RIFM, 1986; RIFM, 1987; RIFM, 1988a)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)

Local Respiratory Toxicity: NOEC = 10 ppm or 61.4 mg/m^3. RIFM (2013b)

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Critical Measured Value: 90% (OECD 301F) RIFM (2012)

Bioaccumulation:
Screening-level: 43.6 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 59.15 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: 59.15 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.05915 μg/L

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

1. Identification

1. **Chemical Name:** α-Methylbenzyl propionate
2. **CAS Registry Number:** 120-45-6
3. **Synonyms:** Benzenemethanol,.α.-methyl-, propanoate; Methylphenylcarbinyl propionate; 1-Phenylethyl propionate; Styralyl propionate; アルキル（C = 1 ~ 5）カルボン酸フェニルアルキル（C = 1 ~ 6）; Styrallyl propionate; α-Methylbenzyl propionate
4. **Molecular Formula:** $C_{11}H_{14}O_2$
5. **Molecular Weight:** 178.23 g/mol
6. **RIFM Number:** 416
7. **Stereochemistry:** Isomer not specified. One stereocenter and a total of 2 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 241.5 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 2.7 (RIFM, 2013a), 2.99 (EPI Suite)
4. **Melting Point**: 10.84 °C (EPI Suite)
5. **Water Solubility:** 157.2 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0274 mm Hg at 20 °C (EPI Suite v4.0), 0.0428 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient (6 L mol^{-1} • cm^{-1}, condition not specified) is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid

3. Volume of use (Worldwide Band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.13% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.0010 mg/kg/day or 0.078 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.0044 mg/kg/day (RIFM, 2021)

*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 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 et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 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 v4.2
I	I	I

2. Analogs Selected:
a. **Genotoxicity:** α-Methylbenzyl acetate (CAS # 93-92-5)
b. **Repeated Dose Toxicity:** α-Methylbenzyl acetate (CAS # 93-92-5)
c. **Reproductive Toxicity:** α-Methylbenzyl acetate (CAS # 93-92-5)
d. **Skin Sensitization:** Benzyl acetate (CAS # 140-11-4)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** Benzyl acetate (CAS # 140-11-4)
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

α-Methylbenzyl propionate is not reported to occur in 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.

9. REACH dossier

α-Methylbenzyl propionate has been pre-registered for 2010; no dossier available as of 02/22/22.

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, α-methylbenzyl propionate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. α-Methylbenzyl propionate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013c). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an equi-reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of α-methylbenzyl propionate; however, read-across can be made to α-methylbenzyl acetate (CAS # 93-92-5; see Section VI).

A mammalian cell gene mutation assay (mouse lymphoma assay) was conducted according to OECD TG 476/GLP guidelines. Mouse lymphoma cells were treated with α-methylbenzyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 1000 μg/mL (as determined in a preliminary toxicity assay) for 3 h and up to 350 μg/mL for 24 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (RIFM, 2019). Under the conditions of the study, α-methylbenzyl acetate was not mutagenic to mammalian cells *in vitro*, and this can be extended to α-methylbenzyl propionate.

The clastogenic activity of α-methylbenzyl propionate 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 α-methylbenzyl propionate in DMSO at concentrations up to 1000 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation. α-Methylbenzyl propionate did not induce binucleated cells with micronuclei in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, α-methylbenzyl propionate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, α-methylbenzyl acetate does not present a concern for genotoxic potential, and this can be extended to α-methylbenzyl propionate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/21.

11.1.2. Repeated dose toxicity

The MOE for α-methylbenzyl propionate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on α-methylbenzyl propionate. Read-across material α-methylbenzyl acetate (CAS # 93-92-5; see Section VI) has sufficient repeated dose toxicity data. In a gavage 13-week subchronic toxicity study, groups of 15 CFE rats/sex/dose were administered via gavage with test material, α-methylbenzyl acetate at doses of 0, 15, 50, or 150 mg/kg/day daily in a corn oil vehicle. One death in the low-dose group and 2 deaths in the mid-dose group occurred, but it was suggested that the deaths were due to inadvertent intratracheal dosing. There were increases in the relative liver (approximately 7%) and kidney (approximately 9%) weights among males of the 150 mg/kg/day dose groups. Necropsy and histopathological examination of the high-dose group showed no adverse effects. Thus, the NOAEL was considered to be 150 mg/kg/day, the highest dosage tested (Gaunt et al., 1974).

Therefore, the α-methylbenzyl propionate MOE can be calculated by dividing α-methylbenzyl acetate NOAEL in mg/kg/day by the total systemic exposure to α-methylbenzyl propionate, 150/0.0044 or 34091.

In addition, the total systemic exposure to α-methylbenzyl propionate (4.4 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/29/21.

11.1.3. Reproductive toxicity

The MOE for α-methylbenzyl propionate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on α-methylbenzyl propionate. Read-across material α-methylbenzyl acetate (CAS # 93-92-5; see Section VI) has sufficient reproductive toxicity data. In an OECD 414/GLP prenatal developmental toxicity study, 22 female Wistar Han rats/group were administered dose levels of 100, 200, and 500 mg/kg/day by oral gavage from gestation days (GDs) 6–20. No treatment-related mortality was observed at any dose groups. A decrease in food consumption was observed at 500 mg/kg/day from days 6–12, which resulted in a slightly lower bodyweight gain on days 9–18. However, as food consumption recovered to normal values during the remainder of the treatment period and as the effect on terminal (gravid) body weight was minimal, this was considered to be non-adverse. Slightly lower fetal body weights were observed at the highest dose level. This slight decrease was considered non-adverse as values were within the available historical control data. No treatment-related toxicologically relevant changes were noted in any of the developmental parameters. Thus, the NOAEL for developmental toxicity was considered to be 500 mg/kg/day, the highest dose tested (RIFM, 2020a).

In another OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were exposed to the test material α-methylbenzyl acetate at dose levels of 0, 100, 200, and 500 mg/kg/day by oral gavage. Males were treated for 29 days (up to and including the day before scheduled necropsy) and females were treated for 50–65 days (2 weeks prior to mating, during mating, and 13 days after delivery, up to and including the day of scheduled necropsy). A statistically significant lower food consumption was noted for females treated at the highest dose during the lactation period, which resulted in lower body weight. There were no treatment-related effects seen in mortality, clinical appearance, T4 thyroid hormone levels, macroscopic examination, organ weights, and microscopic examination. At the highest dose, scales were noted for most pups between PND 1 and 8 and were considered adverse. However, this effect was transient and from PND8 onwards and at necropsy, scales were not observed in any pups. Pup body weights were significantly lower in the highest-dose group as compared to control. No toxicologically significant changes were noted in any of the other developmental parameters at any dose levels. Thus, the NOAEL for developmental toxicity was considered to be 200 mg/kg/day, based on reduced pup body weight (RIFM, 2020b).

Thus, the most conservative developmental toxicity NOAEL of 200 mg/kg/day was selected for this safety assessment.

Therefore, the α-methylbenzyl propionate MOE for the developmental toxicity endpoint can be calculated by dividing the α-methylbenzyl acetate NOAEL in mg/kg/day by the total systemic exposure to α-methylbenzyl propionate, 200/0.0044 or 45455.

There are sufficient fertility data on α-methylbenzyl acetate. In an OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were exposed to the test material α-Methylbenzyl acetate at dose levels of 0, 100, 200, and 500 mg/kg/day by oral gavage. Males were treated for 29 days (up to and including the day before scheduled necropsy) and females were treated for 50–65 days (2 weeks prior to mating, during mating, and 13 days after delivery, up to and including the day of scheduled necropsy). A statistically significant lower food consumption was noted for females treated at the highest dose during the lactation period, which resulted in lower body weight. No treatment-related effects were noted in any of the reproductive parameters examined (mating and fertility indices, precoital time, number of implantations, estrous cycle, and histopathological examination of reproductive organs). Thus, the NOAEL for fertility was considered to be 500 mg/kg/day, the highest dose tested (RIFM, 2020b).

Therefore, the α-methylbenzyl propionate MOE for the fertility endpoint can be calculated by dividing the α-methylbenzyl acetate NOAEL in mg/kg/day by the total systemic exposure to α-methylbenzyl propionate, 500/0.0044 or 113636.

In addition, the total systemic exposure to α-methylbenzyl propionate (4.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/21.

11.1.4. Skin sensitization

Based on the existing data and read-across to benzyl acetate (CAS # 140-11-4), α-methylbenzyl propionate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for α-methylbenzyl propionate. Based on the existing data and read-across to benzyl acetate (CAS # 140-11-4; see Section VI), α-methylbenzyl propionate does not present a concern for skin sensitization under the current, declared levels of use. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In several guinea pig test methods, no reactions indicative of sensitization were observed with read-across material benzyl acetate (RIFM, 1985b; RIFM, 1986; RIFM, 1985a; RIFM, 1985c). No skin sensitization reactions were observed when α-methylbenzyl propionate and read-across material benzyl acetate were tested in human maximization tests (Greif, 1967; RIFM, 1973). Additionally, in several Confirmation of No Induction in Humans tests (CNIHs) up to 8% (9448 $\mu g/cm^2$) of read-across benzyl acetate in 3:1 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of skin sensitization were observed (RIFM, 1987; RIFM, 1988a; RIFM, 1988b; RIFM, 1988c; RIFM, 1988d; RIFM, 1975a; RIFM, 1975b; RIFM, 1975c; RIFM, 1975d; RIFM, 1975e).

Based on weight of evidence (WoE) from structural analysis, human

studies, and data from read-across material benzyl acetate, α-methylbenzyl propionate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/27/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, α-methylbenzyl propionate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for α-methylbenzyl propionate in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, α-methylbenzyl propionate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient (6 L mol^{-1} • cm^{-1}, condition not specified) 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: 07/26/21.

11.1.6. Local respiratory toxicity

There are insufficient inhalation data available on α-methylbenzyl propionate; however, in an acute, 2-week inhalation study for the analog benzyl acetate (CAS # 140-11-4; see Section VI), a NOEC of 10 ppm (61.4 mg/m^3) was reported (RIFM, 2013b).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. A NOAEC of 10 ppm (61.4 mg/m^3) is reported for read-across analog, benzyl acetate, for a 2-week acute study conducted in rats (RIFM, 2013b). At this level, increased lactate dehydrogenase was noted in the bronchoalveolar lavage fluid. Although the authors did not consider these effects as adverse, for the purpose of estimating local respiratory toxicity MOE, the lower exposure dose (61.4 mg/m^3) was considered.

This NOAEC expressed in mg/kg lung weight/day is:

- (61.4 mg/m^3) × (1 m^3/1000 L) = 0.0614 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat* × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- (0.0614 mg/L) × (61.2 L/d) = 3.76 mg/d
- (3.76 mg/d)/(0.0016 kg lung weight of rat**) = 2349 mg/kg/day

The 95th percentile calculated exposure was reported to be 0.078 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015 and Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.12 mg/kg lung weight/day resulting in a MOE of 19575 (i.e., [2349 mg/kg lung weight of rat/day]/[0.12 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.078 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

* Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey=9100R7VE.PDF.

* *Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/13/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of α-methylbenzyl propionate 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, α-methylbenzyl propionate 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 α-methylbenzyl propionate 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 Volume of Use (2015), α-methylbenzyl propionate does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 2012: The ready biodegradability of the test material was evaluated according to the manometric respirometry test following the OECD 301F guidelines. After 28 days, biodegradation of 90% was observed.

11.2.1.3. Ecotoxicity. No data available.

11.2.1.4. Other available data. α-Methylbenzyl propionate has been pre-registered for REACH with no additional data at this time.

11.2.1.5. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.7	2.7
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 0.05915 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 07/28/21.

*11.3. 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's Toxicology Information Services:** 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 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://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 02/22/22.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113442.

Appendix

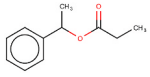
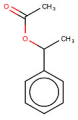
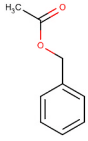
Read-across Justification

Methods

The read-across analog(s) was/were 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 Chemical Agency read-across assessment framework (ECHA, 2017b).

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	59.15			1000000	0.05915	

- 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 v4.2 (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	α-Methylbenzyl propionate	α-Methylbenzyl acetate	Benzyl acetate
CAS No.	120-45-6	93-92-5	140-11-4
Structure			
Similarity (Tanimoto Score)		0.93	0.33
Read-across Endpoint		• Genotoxicity • Repeated dose toxicity • Reproductive toxicity	• Skin sensitization • Local respiratory toxicity
Molecular Formula	$C_{11}H_{14}O_2$	$C_{10}H_{12}O_2$	$C_9H_{10}O_2$
Molecular Weight (g/mol)	178.23	164.21	150.17
Melting Point (°C, EPI Suite)	10.84	−0.17	−0.5
Boiling Point (°C, EPI Suite)	241.50	223.12	215.57
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.7	14.9	0.187
Log Kow (KOWWIN v1.68 in EPI Suite)	2.7	2.5	2.08
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	157.2	481.1	1605
J_{max} (μg/cm^2/h, SAM)	42.612	74.646	64.0
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.53E+000	1.90E+000	1.4337
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	AN2|AN2 ≫ Schiff base formation after aldehyde release|AN2 ≫ Schiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters	
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)	No alert found	No alert found	
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	Not categorized	
Reproductive Toxicity			
ER Binding by OECD QSAR Toolbox (4.2)	Non-binder, without OH or NH2 group	Non-binder	

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Developmental Toxicity Model by CAESAR v2.1.6	Non-toxicant (low reliability)	Toxicant (medium reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom| SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters
Protein Binding (OECD)	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals		SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals
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)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom| SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Acyl Transfer agent identified.		Alert for Acyl Transfer agent identified.
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

Summary

There are insufficient toxicity data on α-methylbenzyl propionate (CAS # 120-45-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, α-methylbenzyl acetate (CAS # 93-92-5) and benzyl acetate (CAS # 140-11-4) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- α-Methylbenzyl acetate (CAS # 93-92-5) was used as a read-across analog for the target material α-methylbenzyl propionate (CAS # 120-45-6) for the genotoxicity, repeated dose toxicity, and reproductive toxicity endpoints.
  - o The target material and the read-across analog belong to the class of aromatic esters.
  - o The key difference between the target material and the read-across analog is that the target material is a propionate ester, whereas the read-across analog has is an acetate ester. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the ethyl benzene fragment. 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 read-across analog has a DNA binding alert by the OASIS QSAR Toolbox model. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. The target material and the read-across analog have Michael addition alert by OECD QSAR toolbox model. There are no other DNA binding alerts. This shows that the read-across analog is predicted to have comparable reactivity with the target material. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genetic toxicity. Therefore, the alert will be superseded by the availability of 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.
- Benzyl acetate (CAS # 140-11-4) was used as a read-across analog for the target material α-methylbenzyl propionate (CAS # 120-45-6) for the skin sensitization and local respiratory toxicity endpoints.
  - o The target material and the read-across analog belong to the class of aromatic esters.
  - o The key difference between the target material and the read-across analog is that the target material has a propionate group on the acid portion, whereas the read-across analog has an acetyl group. Moreover, the target has an additional methyl substituent on the α position. These structural differences are toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the benzene fragment. 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 have several protein binding alerts. Data described in the skin sensitization section above are consistent with *in silico* alerts and show that the read-across analog does not pose a concern for skin sensitization.

- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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