Food and Chemical Toxicology 182 (2023) 114131

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, α,α-dimethylphenethyl butyrate, CAS Registry Number 10094-34-5

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ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

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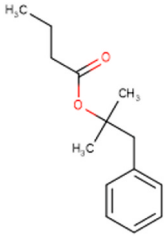
https://doi.org/10.1016/j.fct.2023.114131
Received 5 July 2023; Accepted 24 October 2023
Available online 7 November 2023

Version: 062923. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: α,α-Dimethylphenethyl butyrate
CAS Registry Number: 10094-34-5

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, 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

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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.

α,α-Dimethylphenethyl butyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that α,α-dimethylphenethyl butyrate is not genotoxic. Data on read-across analog 1,1-dimethyl-2-phenylethyl acetate (CAS # 151-05-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog benzyl acetate (CAS # 140-11-4) show that there are no safety concerns for α,α-dimethylphenethyl butyrate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; α,α-dimethylphenethyl butyrate 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 α,α-dimethylphenethyl butyrate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; α,α-dimethylphenethyl butyrate 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, 2001; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 360 mg/kg/day. ECHA (2017c)
Reproductive Toxicity: Developmental toxicity and Fertility NOAEL = 1000 mg/kg/day. ECHA (2017c)
Skin Sensitization: Not a sensitization concern. (RIFM, 2002; RIFM, 1988a; RIFM, 1987)
Photoirritation/Photoallergenicity: Not expected to be a photoirritant/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: 98% (OECD 302C) RIFM (1999b)
Bioaccumulation:
Screening-level: 386.2 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Critical Ecotoxicity Endpoint: 72-h Algae EbC50: 0.86 mg/L RIFM (2013b)
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: 72-h Algae EbC50: 0.86 mg/L RIFM (2013b)
RIFM PNEC is: 0.86 μg/L
- Revised PEC/PNECs (2019 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** α,α-Dimethylphenethyl butyrate
2. **CAS Registry Number:** 10094-34-5
3. **Synonyms:** Benzyl dimethyl carbinyl butyrate; 2-Benzyl-2-propyl butyrate; Butanoic acid, 1,1-dimethyl-2-phenethyl ester; Dimethylbenzyl carbinyl butyrate; DMBC butyrate; 2-Methyl-1-phenyl-2-propyl butyrate; ｱﾙｷﾙ(C = 1～5)ｶﾙﾎﾞﾝ酸ﾌｪﾆﾙｱﾙｷﾙ(C = 1～6); 1,1-Dimethyl-2-phenylethyl butyrate; α,α-Dimethylphenethyl butyrate
4. **Molecular Formula:** $C_{14}H_{20}O_2$

5. **Molecular Weight:** 220.31 g/mol
6. **RIFM Number:** 960
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 285.12 °C (EPI Suite v4.11)
2. **Flash Point:** >93 °C (Globally Harmonized System), 200 °F; closed cup (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 4.5 at 35 °C (RIFM, 1999c), 4.43 (EPI Suite v4.11)
4. **Melting Point**: 49.18 °C (EPI Suite v4.11)
5. **Water Solubility:** 5.701 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 0.972 (FMA)
7. **Vapor Pressure:** 0.00141 mm Hg at 20 °C (EPI Suite v4.0), 0.006 mm Hg at 20 °C (FMA), 0.00257 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:** Colorless liquid with a mild, herbaceous odor

3. Volume of use (Worldwide band)

1.100–1000 metric tons per year (IFRA, 2019).

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.2.9)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.18% (RIFM, 2020)
2. **Inhalation Exposure*:** 0.00082 mg/kg/day or 0.060 mg/day (RIFM, 2020)
3. **Total Systemic Exposure**:** 0.0016 mg/kg/day (RIFM, 2020)

*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:** 13.3%, read-across from 1,1-dimethyl-2-phenylethyl acetate (DPA; CAS # 151-05-3)

RIFM, 2015**:** A study was designed to determine the *in vitro* human skin permeation rate and distribution of read-across analog 1,1-dimethyl-2-phenylethyl acetate (DPA; CAS # 151-05-3; see Section VI). Application (5 μL/cm^2) was in 70/30 (v/v) ethanol/water under both unoccluded and occluded conditions at a target concentration of 1.5% (measured concentration 1.59%). Twelve active dosed diffusion cells were prepared (using 4 donors) for both unoccluded and occluded conditions, plus 4 control cells (1 per donor, unoccluded). Epidermal membranes (from female abdominal skin) were used, and integrity was assessed by measuring electrical resistance. Permeation of DPA, from a 5 μL/cm^2 dose of a 1.59% (w/v) solution, was then measured at 12 time points over 24 h, using a pH 7.4 phosphate-buffered saline (PBS) receptor phase. For the occluded group, chambers were occluded using greased glass coverslips applied immediately following application. At 24 h, the epidermal membranes were wiped, the tape was stripped 10 times, and the DPA content of the wipes, strips, and remaining epidermis was determined. Filter paper skin supports were extracted, and diffusion cell donor chambers and glass coverslips (for the occluded group) were wiped to remove sealing grease and then washed. These samples were analyzed so that mass balance could be performed. Evaporative loss of DPA was estimated by measuring the loss from PTFE sheets under the same conditions. Sensitive UHPLC-UV methods were developed for the analysis of DPA in receptor phase and skin distribution samples. At 24 h, 3.47 ± 0.40 and 9.61 ± 1.01 μg/cm^2 DPA had permeated under unoccluded and occluded conditions, which corresponds to 4.36% ± 0.50% and 12.1% ± 1.3% of the applied dose, respectively. Occluded conditions not only reduce the loss of volatile application vehicles and test compounds but also increase skin hydration, and these factors caused an increase in the permeation of DPA compared to unoccluded conditions. Overall recoveries of the applied DPA were low at 8.42% ± 0.73% and 54.3% ± 2.0% of the dose for unoccluded and occluded conditions, respectively. The investigation of evaporative loss from PTFE sheets mounted in diffusion cells showed that evaporation was rapid (50% recovered at 1 h, 19% recovered at 2 h, and none recovered at 6 h and beyond). The overall skin absorption values, defined as amounts that have permeated and amounts in the epidermis (therefore excluding tape strips) and skin support, were 3.96 ± 0.41 and 10.5 ± 1.1 μg/cm^2, for the unoccluded and occluded groups, respectively, corresponding to 4.98% ± 0.52% and 13.3% ± 1.3% of the applied dose.

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:** 1,1-Dimethyl-2-phenylethyl acetate (CAS # 151-05-3)
   c. **Reproductive Toxicity:** 1,1-Dimethyl-2-phenylethyl acetate (CAS # 151-05-3)
   d. **Skin Sensitization:** Benzyl acetate (CAS # 140-11-4); Weight of Evidence (WoE) material: 2-Phenoxyethyl isobutyrate (CAS # 103-60-6)
   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

α,α-Dimethylphenethyl butyrate 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

Available (ECHA, 2017c); accessed 09/30/22.

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,α-dimethylphenethyl butyrate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. α,α-Dimethylphenethyl butyrate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity with and without metabolic activation (RIFM, 2013a). 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 α,α-dimethylphenethyl butyrate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with α,α-dimethylphenethyl butyrate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2001). Under the conditions of the study, α,α-dimethylphenethyl butyrate was not mutagenic in the Ames test.

The clastogenic activity of α,α-dimethylphenethyl butyrate 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,α-dimethylphenethyl butyrate in DMSO at concentrations up to 2203 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 300 μg/mL in the presence and absence of metabolic activation. α,α-Dimethylphenethyl butyrate did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, α,α-dimethylphenethyl butyrate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, α,α-dimethylphenethyl butyrate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/11/22.

11.1.2. Repeated dose toxicity

The MOE for α,α-dimethylphenylethyl butyrate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on α,α-dimethylphenylethyl butyrate. Read-across material 1,1-dimethyl-2-phenylethyl acetate (CAS # 151-05-3; see Section VI) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint.

There are sufficient repeated dose toxicity studies on 1,1-dimethyl-2-phenylethyl acetate that can be used to support the repeated dose toxicity endpoint. An OECD 408- and GLP-compliant (90-day oral toxicity study) test was conducted in Sprague Dawley rats. Groups of 10 rats/sex/dose were administered test material 1,1-dimethyl-2-phenylethyl acetate via oral gavage in 0.1% Tween 80 at doses of 0, 90, 180, or 360 mg/kg/day. In addition, there was also a high-dose recovery group of 5 males and females. No statistically significant changes in mean body weight and mean bodyweight gain were observed during the treatment period in males and females. A transient clinical sign of diarrhea was observed in all the treated groups. No adverse effects were seen in hematological findings, clinical biochemistry, and urinalysis. Further, no treatment-related adverse effects were observed with respect to organ weights, gross pathology, and histopathology. Thus, based on overall observations, the NOAEL was considered to be 360 mg/kg/day, the highest dose tested (ECHA, 2017c).

Another OECD 422- and GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test was also conducted in Wistar Han rats. Groups of 10 male and 13 female rats/dose were administered test material 1,1-dimethyl-2-phenylethyl acetate at doses of 250, 500, and 1000 mg/kg/day via oral gavage in corn oil. Males were treated for 14 days pre-mating, during mating, and post-mating till 28 days, and females were treated for 14 days pre-mating, during mating, and at least 13 days after delivery. During the study, no animal mortality was reported. No treatment-related adverse

Table 1
Summary of existing data on benzyl acetate as a read-across for α,α-Dimethylphenethyl butyrate.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
No evidence of sensitization[g]	9448	5520	N/A	N/A	N/A	Negative	Negative
	***In vitro* Data[f]**				***In silico* protein binding alerts (OECD Toolbox v4.5)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	N/A	N/A	N/A		SN2	SN2	SN2

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

[a] 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).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Based on animal data using classification defined in ECETOC (ECETOC, 2003).

[e] Studies conducted according to the OECD TG 406 are included in the table.

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

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

effects were reported for urinalysis, hematology, blood chemistry, and sensory function. A slight decrease in bodyweight gain during the pre-mating (both males and females) and mating periods (only males) was observed at the highest dose. Reddening and abscess in the lungs and enlargement of mediastinal lymph nodes were also observed. However, as these findings were not dose dependent and also presented in animals from the control group, they were considered to be unrelated to treatment. No adverse effects were seen in hematological findings, clinical biochemistry, and urinalysis. Further, no treatment-related adverse effects were observed with respect to organ weights, gross pathology, and histopathology. Thus, the NOAEL was considered to be 500 mg/kg/day, based on a decrease in bodyweight gains seen at the highest dose (ECHA, 2017c).

Considering both OECD 408 and OECD 422 studies, a more robust NOAEL of 360 mg/kg/day from OECD 408 (90-day study) was considered for the safety assessment.

Therefore, the α,α-dimethylphenylethyl butyrate MOE for the repeated dose toxicity endpoint can be calculated by dividing the 1,1-dimethyl-2-phenylethyl acetate NOAEL in mg/kg/day by the total systemic exposure for α,α-dimethylphenylethyl butyrate, 360/0.0016 or 225000.

In addition, the total systemic exposure to α,α-dimethylphenylethyl butyrate (1.6 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: 11/11/22.

11.1.3. Reproductive toxicity

The MOE for α,α-dimethylphenylethyl butyrate 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,α-dimethylphenylethyl butyrate. Read-across material 1,1-dimethyl-2-phenylethyl acetate (CAS # 151-05-3; see Section VI) has sufficient developmental toxicity and fertility data to support the reproductive toxicity endpoint.

An OECD 422- and GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 male and 13 female rats/dose were administered test material 1,1-dimethyl-2-phenylethyl acetate at doses of 250, 500, and 1000 mg/kg/day via oral gavage in corn oil. Males were treated for 14 days pre-mating, during mating, and post-mating till 28 days, and females were treated for 14 days pre-mating, during mating, and at least 13 days after delivery. During the study, no animal mortality was reported. There were no treatment-related effects on any mating and fertility parameters in the P-generation males and females at any dose. No treatment-related effects were seen in estrous cycling or litter parameter in the P-generation females at any dose. In the F1 generation pups, there were no treatment-related clinical observations or effects on anogenital distance, nipple retention (males), or mean pup body weights at any dose. In addition, there were no treatment-related macroscopic or microscopic observations in the F1 generation pups at any dose. Based on no effects seen up to the highest dose, the NOAEL for this study was determined to be 1000 mg/kg/day (ECHA, 2017c).

In another OECD 414/GLP prenatal developmental toxicity study, 25 female Sprague Dawley rats/group were administered dose levels of 0 and 1000 mg/kg/day in 0.1% Tween 80 via oral gavage from gestation days (GDs) 5–19. No mortality was observed. No treatment-related changes in body weight, bodyweight gain, and feed consumption were observed in females. No gross lesions were observed in dams during necropsy in any of the doses tested. No treatment-related or toxicologically relevant effects were seen in fetuses with respect to external, visceral, and skeletal examinations. Thus, the NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, based on the absence of treatment-related adverse effects on the development of pups up to the highest dose tested (ECHA, 2017c).

Therefore, the α,α-dimethylphenylethyl butyrate MOE for the developmental toxicity and fertility endpoint can be calculated by dividing the 1,1-dimethyl-2-phenylethyl acetate NOAEL in mg/kg/day by the total systemic exposure for α,α-dimethylphenylethyl butyrate, 1000/0.0016 or 625000.

In addition, the total systemic exposure to α,α-dimethylphenylethyl butyrate (1.6 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: 11/11/22.

11.1.4. Skin sensitization

Based on the existing data on the target material, read-across material benzyl acetate, and WoE material 2-phenoxyethyl isobutyrate, α,α-dimethylphenethyl butyrate presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for α,α-dimethylphenethyl butyrate. Therefore, benzyl acetate (CAS # 140-11-4; see Section VI) was used for the risk assessment of α,α-dimethylphenethyl butyrate. The data on the read-across material are summarized in Table 1. Additionally, 2-phenoxyethyl isobutyrate was used as WoE (CAS # 103-60-6; see Section VI). Based on the existing data on the read-across and WoE materials, α,α-dimethylphenethyl butyrate is not considered a skin sensitizer. The chemical structure of the WoE material and the target material indicate that they would not be expected to react with skin proteins directly. However, the read-across material is predicted to react to skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). In a murine local lymph node assay (LLNA), WoE material 2-phenoxyethyl isobutyrate was found to be non-sensitizing when tested up to 100% (25000 μg/cm^2) (RIFM, 2002). In a guinea pig maximization test, read-across material benzyl acetate did not lead to skin sensitization reactions (RIFM, 1985b). A guinea pig Buehler test did not present reactions indicative of sensitization in the read-across material (RIFM, 1986a). In human maximization tests, no skin sensitization reactions were observed with the target, read-across, or WoE materials (RIFM, 1977; Greif, 1967; RIFM, 1973). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 9448 μg/cm^2 of read-across material benzyl acetate in 1:3 ethanol: diethyl phthalate found no reactions indicative of sensitization observed in any of the 108 or 197 volunteers (RIFM, 1988a; RIFM, 1987). In other CNIHs with the read-across or WoE materials, no reactions indicative of sensitization were observed (RIFM, 1975e; RIFM, 1965).

Based on WoE from structural analysis and animal and human studies on the read-across and WoE materials as well as the target material, α,α-dimethylphenethyl butyrate does not present a concern for skin sensitization.

Additional References: RIFM, 1988b; RIFM, 1988c; RIFM, 1988d; RIFM, 1975a; RIFM, 1975b; RIFM, 1975c; RIFM, 1975d; RIFM, 1961; RIFM, 1962; Klecak, 1979; RIFM, 1985a; Ishihara et al., 1986; RIFM, 1985c; Klecak (1985); RIFM, 1967; RIFM, 1986b.

Literature Search and Risk Assessment Completed On: 11/10/22.

11.1.5. Photoirritation/photoallergenicity

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.986			1000000	0.001986	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.129	1.810	0.525	10000	0.0525	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.201	0.853	1.604			Neutral Organics SAR (baseline toxicity)
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	>2.7					
Daphnia		1.2				
Algae		0.86		1000	0.86	

11.1.5.1. Risk assessment. There are no photoirritation or photoallergy studies available for α,α-dimethylphenethyl butyrate in experimental models. UV/Vis absorption 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). Based on the lack of absorbance, α,α-dimethylphenethyl butyrate 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 effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/31/22.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on α,α-dimethylphenethyl butyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.060 mg/day. This exposure is 23.3 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: 11/08/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of α,α-dimethylphenethyl butyrate 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, α,α-dimethylphenethyl butyrate was identified as a fragrance material with the 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 identify α,α-dimethylphenethyl butyrate as possibly being persistent but not 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, 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 $\geq$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), α,α-dimethylphenethyl butyrate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. **RIFM, 2000:** The ready biodegradability of the test material was evaluated according to the OECD 301D guidelines. 2.7 mg/L of α,α-dimethylphenethyl butyrate was incubated in the dark at approximately 20 ± 1 °C using a water bath under aerobic conditions for 28 days.

RIFM, 1999a: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. The test material underwent 85% biodegradation after 34 days (82% after 28 days) in the test conditions.

RIFM, 1999b: The inherent biodegradability of the test material was determined by the Respirometric Method according to the OECD 302C method. Test material underwent 99% biodegradation after 33 days (and 98% after 28 days) in the test conditions.

11.2.1.2.2. Ecotoxicity. **RIFM, 2013c:** An acute *Daphnia magna* toxicity test was conducted according to the OECD 202 method. The 48-h EC50 was reported to be 1.2 mg/L based on the mean measured concentration.

RIFM, 2013d: A 96-h fish (*Pimephales promelas*) acute toxicity test was conducted according to the OECD 203 guidelines. The LC50 was reported to be > 2.7 mg/L based on the mean measured concentration.

RIFM, 2013b: An acute algae toxicity test was conducted according to the OECD 201 guidelines. The 72-h EC50s were reported to be 0.86 mg/L, 1.9 mg/L, and 1.2 mg/L for the area under the growth curve, growth rate, and yield, respectively.

11.2.1.2.3. Other available data. α,α-Dimethylphenethyl butyrate has been pre-registered under REACH with no additional data at this time.

11.2.1.3. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.5	4.5
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on available data, the RQ for this material is < 1. No additional assessment is necessary.

The RIFM PNEC is 0.86 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 11/07/22.

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'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 06/29/23.

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 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.2023.114131.

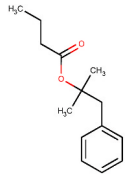
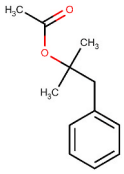
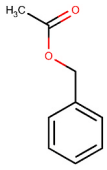
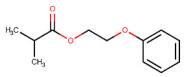
Appendix

Read-across Justification

Methods

The read-across analogs 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 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, 2021).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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	Read-across Material	WoE Material
	α,α-Dimethylphenethyl butyrate	1,1-Dimethyl-2-phenylethyl acetate	Benzyl acetate	2-Phenoxyethyl isobutyrate
CAS No.	10094-34-5	151-05-3	140-11-4	103-60-6
Structure				
Similarity (Tanimoto Score)		0.86	0.33	0.24
SMILES	CCCC(=O)OC(C)(C)Cc1ccccc1	CC(=O)OC(C)(C)Cc1ccccc1	CC(=O)OCc1ccccc1	CC(C)C(=O)OCCOc1ccccc1
Endpoint		Repeated dose toxicity Reproductive toxicity	Skin sensitization	Skin sensitization
Molecular Formula	$C_{14}H_{20}O_2$	$C_{12}H_{16}O_2$	$C_9H_{10}O_2$	$C_{12}H_{16}O_3$
Molecular Weight	220.312	192.258	150.177	208.257
Melting Point (°C, EPI Suite)	49.18	28.29	−51.30	37.71
Boiling Point (°C, EPI Suite)	285.12	252.16	213.00	276.18
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.43E-01	2.97E+00	2.36E+01	7.01E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.70E+00	5.49E+01	3.10E+03	1.06E+02
Log KOW	4.43	3.44	1.96	3.01
J_{max} (μg/cm^2/h, SAM)	0.59	3.51	64.04	2.69
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.92E+00	3.35E+00	1.14E+00	1.80E-01
Repeated Dose Toxicity				
Repeated Dose (HESS)	Not categorized	Toluene (Renal toxicity) Alert		
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.5)	Non-binder, without OH or NH2 group	Non-binder, without OH or NH2 group		
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)		
Skin Sensitization				
Protein Binding (OASIS v1.1)	No alert found		SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters	No alert found
Protein Binding (OECD)	No alert found		SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)		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		SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified.		Alert for Acyl Transfer agent identified.	No skin sensitization reactivity domain alerts identified.
Metabolism				

(*continued on next page*)

(*continued*)

Principal Name	Target Material	Read-across Material	Read-across Material	WoE Material
	α,α-Dimethylphenethyl butyrate	1,1-Dimethyl-2-phenylethyl acetate	Benzyl acetate	2-Phenoxyethyl isobutyrate
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on α,α-dimethylphenethyl butyrate (CAS # 10094-34-5). 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, 1,1-dimethyl-2-phenylethyl acetate (CAS # 151-05-3) and benzyl acetate (CAS # 140-11-4) were identified as read-across analogs and 2-phenoxyethyl isobutyrate (CAS # 103-60-6) was identified as a WoE analog, with sufficient data for toxicological evaluation.

Conclusions

- 1,1-Dimethyl-2-phenylethyl acetate (CAS # 151-05-3) was used as a read-across analog for the target material α,α-dimethylphenethyl butyrate (CAS # 10094-34-5) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the aromatic ester group.
  - o The key difference between the target material and the read-across analog is the target material has 2 additional carbon on the acid side of the ester compared to the read-across analog. 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 The target material has no alerts for repeated dose toxicity, while the read-across analog has an alert for renal toxicity. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. The data on the read-across analog confirms that the material does not pose a concern for repeated dose toxicity. 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* alert and predictions are superseded by the data.
  - o Neither the target material nor the read-across analog has alerts for reproductive toxicity. The data on the read-across analog confirms that the material does not pose a concern for reproductive toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the lack of *in silico* alerts and predictions are superseded by 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,α-dimethylphenethyl butyrate (CAS # 10094-34-5) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the aromatic ester group.
  - o The key difference between the target material and the read-across analog is the target material has an additional carbon between the benzene ring and the ester, as well as 2 methyl substitutions that are not present in the read-across analog. 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 Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the material, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - 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 The target material has no alerts for skin sensitization, while the read-across analog has alerts for SN2 reactions at sp3 carbons for protein binding from OASIS v1.1 and OECD. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. The data on the read-across analog confirms that the material is not a skin sensitizer. 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* alert and predictions are superseded by 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.
- 2-Phenoxyethyl isobutyrate (CAS # 103-60-6) was used as a WoE analog for the target material α,α-dimethylphenethyl butyrate (CAS # 10094-34-5) for the skin sensitization endpoint.
  - o The target material and the WoE analog are structurally similar and belong to the aromatic ester group.

- The key difference between the target material and the WoE analog is the WoE analog has an ether linkage between the benzene ring and the ester group that is not present in the target material. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the WoE analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the WoE analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the WoE analog.
- Neither the target material nor the WoE analog has alerts for skin sensitization. The data on the read-across analog confirms that the material is not a skin sensitizer. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the lack of *in silico* alerts is consistent with the data.
- The target material and the WoE 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 WoE analog and the target material.

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