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Short Review

RIFM fragrance ingredient safety assessment, 2-methyl-4-phenyl-2-butanol, CAS Registry Number 103-05-9

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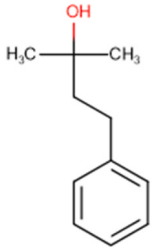


Name: 2-Methyl-4-phenyl-2-butanol
CAS Registry Number: 103-05-9

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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
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; B. Safford et al., 2015; B. Safford et al., 2024; B. 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
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

(*continued on next column*)

(*continued*)

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.

2-Methyl-4-phenyl-2-butanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-methyl-4-phenyl-2-butanol is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 2-methyl-4-phenyl-2-butanol is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog benzenepropanol, alpha, gamma, gamma-trimethyl- (CAS # 2035-93-0) show that there are no safety concerns for 2-methyl-4-phenyl-2-butanol for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-methyl-4-phenyl-2-butanol is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; 2-methyl-4-phenyl-2-butanol 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. ECHA (2018)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: Not a concern for skin sensitization. ECHA (2016)
Photoirritation/Photoallergenicity: Not expected to be a photoirritant/photoallergen. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEL available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 53.7% (OECD 310) RIFM (2015)
Bioaccumulation:
Screening-level: 39.76 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Critical Ecotoxicity Endpoint: *Daphnia Magna* EC50: 12.22 mg/L (ECOSAR v2.0; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: *Daphnia Magna* EC50: 12.22 mg/L (ECOSAR v2.0; US EPA, 2012b)
RIFM PNEC is: 1.22 µg/L
- Revised PEC/PNECs (2019 IFRA VoU): North America and Europe: <1

1. Identification

1. **Chemical Name:** 2-Methyl-4-phenyl-2-butanol
2. **CAS Registry Number:** 103-05-9
3. **Synonyms:** Butanol, 2-methyl-4-phenyl-; Dimethylphenylethyl carbinol; 1,1-Dimethyl-3-phenyl-1-propanol; α,α-Dimethyl-γ-phenylpropyl alcohol; Phenyl ethyl dimethyl carbinol; Dimethyl Phenyl

Ethyl Carbinol; Benzyl-tert-butanol; Dimethylbenzenepropanol; 2-Phenethyl-2-propanol; 2-Methyl-4-phenylbutan-2-ol; 1,1-Dimethyl-3-phenylpropanol; 2-Butanol, 2-methyl-4-phenyl; Phenylethyl dimethyl carbinol; Methyl phenylbutanol; 2-Methyl-4-phenyl-2-butanol

4. **Molecular Formula:** $C_{11}H_{16}O$
5. **Molecular Weight:** 164.24 g/mol
6. **RIFM Number:** 388
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** >200 °C (Fragrance Materials Association [FMA]), 246.89 °C (EPI Suite v4.11)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; closed cup (FMA)
3. **Log K_{OW}:** 2.93 (EPI Suite v4.11)
4. **Melting Point**: 30.36 °C (EPI Suite v4.11)
5. **Water Solubility:** 667.7 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 0.958–0.962 (FMA), 0.960–0.964 (FMA)
7. **Vapor Pressure:** 0.0023 mm Hg at 20 °C (EPI Suite v4.0), 0.009 mm Hg at 20 °C (FMA), 0.00398 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A low melting white crystalline/solid remaining supercooled as a clear, colorless to pale yellow liquid having a floral odor

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.26% (RIFM, 2023)
2. **Inhalation Exposure*:** 0.00071 mg/kg/day or 0.050 mg/day (RIFM, 2023)
3. **Total Systemic Exposure**:** 0.0064 mg/kg/day (RIFM, 2023)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; 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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; 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 v4.5 (OECD, 2021b)
I	I	I

2. Analogs Selected:

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Benzenepropanol, alpha, gamma, gamma-trimethyl- (CAS # 2035-93-0) and Weight of Evidence (WoE) material 4-cyclohexyl-2-methyl-2-butanol (CAS # 83926-73-2)
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

2-Methyl-4-phenyl-2-butanol 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; accessed on 06/16/23.

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, 2-methyl-4-phenyl-2-butanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-Methyl-4-phenyl-2-butanol was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013b). 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 2-methyl-4-phenyl-2-butanol 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA97a, and TA102 were treated with 2-methyl-4-phenyl-2-butanol 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 (ECHA, 2018). Under the conditions of the study, 2-methyl-4-phenyl-2-butanol was not mutagenic in the Ames test.

The clastogenicity of 2-methyl-4-phenyl-2-butanol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with 2-methyl-4-phenyl-2-butanol in DMSO at concentrations up to 2000 μg/mL in the dose range finding study; the main study was conducted at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2018). Under the conditions of the study, 2-methyl-4-phenyl-2-butanol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, 2-methyl-4-phenyl-2-butanol does not present a concern for genotoxic potential.

Additional References: RIFM, 2013b, RIFM, 2013a; Florin et al., 1980; Tachibana and Yonei, 1985; Norppa and Vainio, 1983; Tachibana et al., 1982; Urban and Wyss, 1969; Brunner and Treick, 1982; Rosenkranz and Leifer, 1980; Tomiyama et al., 1986; Mendelson and Fraser, 1965; Cleaver and Painter, 1975; Lilley and Brewer, 1953

Literature Search and Risk Assessment Completed On: 09/01/23.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-methyl-4-phenyl-2-butanol or any read-across materials. The total systemic exposure to 2-methyl-4-phenyl-2-butanol is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 2-methyl-4-phenyl-2-butanol or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-methyl-4-phenyl-2-butanol (6.4 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: 08/23/23.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2-methyl-4-phenyl-2-butanol or any read-across materials. The total systemic exposure to 2-methyl-4-phenyl-2-butanol is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on 2-methyl-4-phenyl-2-butanol or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-methyl-4-phenyl-2-butanol (6.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/23/23.

11.1.4. Skin sensitization

Based on the existing data on the target material, read-across material benzenepropanol, alpha, gamma, gamma-trimethyl-, and WoE material 4-cyclohexyl-2-methyl-2-butanol, 2-methyl-4-phenyl-2-butanol presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for 2-methyl-4-phenyl-2-butanol. Therefore, benzenepropanol, alpha, gamma, gamma-trimethyl- (CAS # 2035-93-0; see Section VI) and WoE material 4-cyclohexyl-2-methyl-2-butanol (CAS # 83926-73-2; see Section VI) were used for the risk assessment of 2-methyl-4-phenyl-2-butanol. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, 2-methyl-4-phenyl-2-butanol is not considered a skin sensitizer. 2-Methyl-4-phenyl-2-butanol, read-across material, and WoE material are predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). 2-Methyl-4--phenyl-2-butanol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA), inconclusive in KeratinoSens, and positive in a human cell line activation test (h-CLAT) (RIFM, 2017d; RIFM, 2017e; RIFM, 2017f). The results were evaluated following the OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021aa), and, due to inconclusive results, 2-methyl-4-phenyl-2-butanol has no conclusion based on the 2 out of 3 Defined Approach. In a murine local lymph node assay (LLNA), read-across material benzenepropanol, alpha, gamma, gamma-trimethyl- was found to be non-sensitizing up to 100% (25000 μg/cm^2) (ECHA, 2016). In a guinea pig maximization test, WoE material 4-cyclohexyl-2-methyl-2-butanol did not lead to skin sensitization reactions (RIFM, 1994). In a human maximization test, no skin sensitization reactions were observed when 2-Methyl-4-phenyl-2-butanol was tested at 2760 μg/cm^2 (RIFM, 1973). Additionally, in a Confirmation of No Induction in Humans (CNIH) test with 4000 μg/cm^2 of WoE material 4-cyclohexyl-2-methyl-2-butanol in petrolatum, no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1985).

Based on WoE from structural analysis and *in vitro*, animal, and human studies on the read-across material, WoE material, and target material, 2-methyl-4-phenyl-2-butanol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/03/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, 2-methyl-4-phenyl-2-butanol would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for 2-methyl-4-phenyl-2-butanol 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, 2-methyl-4-phenyl-2-butanol 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. As such, it is not a concern for photoirritant or photoallergenic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/26/23.

Table 1
Summary of existing data on Benzenepropanol, alpha, gamma, gamma-trimethyl- as a read-across for 2-Methyl-4-phenyl-2-butanol.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL (induction) µg/cm²	WoE NESIL µg/cm²	LLNA[2] Weighted Mean EC3 Value µg/cm²	GPMT	Buehler
No evidence of sensitization[3]	N/A	N/A	N/A	N/A	Negative up to 25000 (100%)	N/A	N/A
	In vitro Data[6]				*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		No alert found	No alert found	Nucleophilic addition

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available.
1WoE 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).
2Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (European Centre for Ecotoxicology and Toxicology of Chemicals, 2003).
3Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2-methyl-4-phenyl-2-butanol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available in the database. Based on the Creme RIFM Model, the inhalation exposure would be 0.051 mg/kg/day, which is 27.5 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: The Union of German Candle Manufacturers, 1997.

Literature Search and Risk Assessment Completed On: 08/22/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-methyl-4-phenyl-2-butanol 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 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, 2-methyl-4-phenyl-2-butanol 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) identified 2-methyl-4-phenyl-2-butanol as possibly 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 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 $\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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	34.38			1000000	0.0343	
ECOSAR Acute Endpoints **(Tier 2) *v2.0***	19.76	12.22	12.98	10000	1.222	Neutral Organics

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), 2-methyl-4-phenyl-2-butanol 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, 2015:** The ready biodegradability of 2-methyl-4-phenyl-2-butanol was evaluated in the headspace test according to the OECD 310 method. Inoculated test medium was dosed with 20 mg C/L of the test material as the nominal sole source of organic carbon. Biodegradation of 53.7% was observed after 28 days.

11.2.1.2.2. Ecotoxicity. **RIFM, 2017a:** The acute toxicity of the test material was assessed using zebrafish (*Brachydanio rerio),* according to the OECD 203 method, under static conditions. Under the conditions of the study, the 96-h LC50 was reported to be 69.57 mg/L (nominal) (95 % conf. limits: 53.02–96.89 mg/L).

RIFM, 2017b: An algae growth inhibition test was conducted according to the OECD 201 method. Under the conditions of the study, the 72-h ErC50 (growth rate) was reported to be > 100 mg/L, and the EyC50 (yield) was reported to be 49.81 mg/L.

RIFM, 2017c: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. Under the conditions of the study, the 48-h EC50 was reported to be greater than 100.0 mg/L.

11.2.1.2.3. Other available data. 2-Methyl-4-phenyl-2-butanol has been registered for REACH with no additional data at this time.

11.2.1.3. Risk assessment refinement. Since 2-methyl-4-phenyl-2-butanol has passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.93	2.93
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	10–100	10–100
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 1.22 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: 08/16/23.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/18/24.

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.2024.114712.

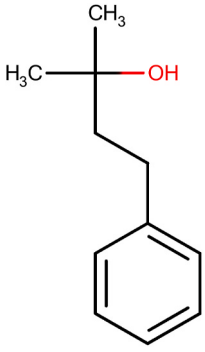
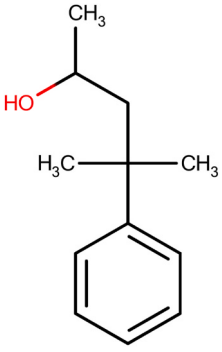
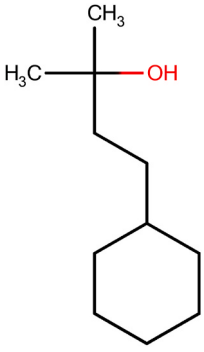
Appendix

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

	Target Material	Read-across Material	WoE Material
Principal Name	2-Methyl-4-phenyl-2-butanol	benzenepropanol, α,γ,γ-trimethyl-	4-Cyclohexyl-2-methyl-2-butanol
CAS No.	103-05-9	2035-93-0	83926-73-2
Structure			
Similarity (Tanimoto Score)		0.89	0.25
SMILES	CC(C)(O)CCc1ccccc1	CC(O)CC(C)(C)c1ccccc1	CC(C)(O)CCC1CCCCC1
Endpoint		Skin sensitization	Skin sensitization
Molecular Formula	$C_{11}H_{16}O$	$C_{12}H_{18}O$	$C_{11}H_{22}O$
Molecular Weight	164.248	178.275	170.296
Melting Point (°C, EPI Suite)	24.50	32.85	16.60
Boiling Point (°C, EPI Suite)	246.89	261.81	232.34
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.31E-01	1.72E-01	1.33E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	6.68E+02	2.52E+02	7.89E+01
Log KOW	2.93	3.35	3.98
J_{max} (μg/cm^2/h, SAM)	40.02	18.81	10.91
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	6.84E-02	9.08E-02	2.05E+00
Protein Binding (OASIS v1.1)	No alert found	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found	No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	WoE Material
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	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified	No skin sensitization reactivity domain alerts identified	No skin sensitization reactivity domain alerts identified
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 2-methyl-4-phenyl-2-butanol (CAS # 103-05-9). 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, 4-methyl-4-phenylpentan-2-ol (CAS # 2035-93-0) was identified as a read-across analog and 4-cyclohexyl-2-methyl-2-butanol (CAS # 83926-73-2) was identified as a WoE material with sufficient data for toxicological evaluation.

Conclusions

- 4-Methyl-4-phenylpentan-2-ol (CAS # 2035-93-0) was used as a read-across analog and 4-cyclohexyl-2-methyl-2-butanol (CAS # 83926-73-2) was used as a WoE material for the target material, 2-methyl-4-phenyl-2-butanol (CAS # 103-05-9), for the skin sensitization endpoint.
  - o The target material and the read-across analog share a commonality in that they are both phenyl alcohols.
  - o The key difference between the target material and the read-across analog is that the read-across material is a secondary alcohol, whereas the target material is a tertiary alcohol. Therefore, to satisfy the structural domain of the target material, substance 4-Cyclohexyl-2-methyl-2-butanol (CAS # 83926-73-2) is used as WoE. This chemical has a tertiary alcohol and a similar structure motif such as the target material. The read-across analog, combined with the WoE material, contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog do not display *in silico* alerts for the skin sensitization endpoint. Data for the read-across analog indicates that it is not a concern for skin sensitization. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are consistent with the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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