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Short Review

RIFM fragrance ingredient safety assessment, 2,2-dimethyl-3-phenylpropanol, CAS registry number 13351-61-6

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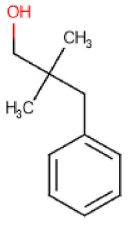

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Abbreviation/Definition List:

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

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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, 2024) 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

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.

2,2-Dimethyl-3-phenylpropanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 2,2-dimethyl-3-phenylpropanol is not genotoxic. Data on read-across analog β-methylphenethyl alcohol (CAS # 1123-85-9) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across analog 3-phenyl-1-propanol (CAS # 122-97-4) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data from read-across analog 2-methyl-5-phenylpentanol (CAS # 25634-93-9) show that there are no safety concerns for 2,2-dimethyl-3-phenylpropanol for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2,2-dimethyl-3-phenylpropanol is not expected to be photoirritating/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog phenethyl alcohol (CAS # 60-12-8). The environmental endpoints were evaluated; 2,2-dimethyl-3-phenylpropanol 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, 2008a; RIFM, 2008b)
Repeated Dose Toxicity: NOAEL = 40 mg/kg/day. (Gaunt et al., 1982)
Reproductive Toxicity: Developmental NOAEL = 300 mg/kg/day. Fertility NOAEL = 1000 mg/kg/day. (RIFM, 2016)
Skin Sensitization: Not a concern for skin sensitization. (RIFM, 1988)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic. (UV/Vis Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 5.0 mg/m^3 (RIFM, 2013)
Environmental Safety Assessment
Hazard Assessment:
Persistence:
Critical Measured Value: 15.2% (BODIS) (RIFM, 1995)
Bioaccumulation:
Screening-level: 22.07 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 34.33 mg/L (Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 34.33 mg/L (Salvito et al., 2002)
RIFM PNEC is: 0.00343 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable cleared at the screening-level

1. Identification

1. **Chemical Name:** 2,2-Dimethyl-3-phenylpropanol
2. **CAS Registry Number:** 13351-61-6
3. **Synonyms:** Benzenepropanol, .β.,.β.-dimethyl-; Dimethyl-3-Phenylpropanol; Benzenepropanol, β,β-dimethyl-; 1-Propanol, 2,2-dimethyl-3-phenyl-; Dimethyl phenylpropanol; Muguetalcohol; 2,2-Dimethyl-3-phenylpropan-1-ol; Farnesol KS; 2,2-Dimethyl-3-phenylpropanol
4. **Molecular Formula:** $C_{11}H_{16}O$
5. **Molecular Weight:** 164.24 g/mol
6. **RIFM Number:** 5399
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 260.56 °C (EPI Suite v4.11), 246–247 °C corrected to 1013 hPa (RIFM, 2015e)
2. **Flash Point:** >93 °C (Globally Harmonized System), 117.5 °C (corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015b)
3. **Log K_{OW}:** 2.93 (EPI Suite v4.11), 2.24 at 23.8 °C (RIFM, 2015d)
4. **Melting Point**: 34.35 °C (EPI Suite v4.11)
5. **Water Solubility:** 667.7 mg/L at 25 °C (EPI Suite v4.11), 1.49 g/L at 20 ± 0.5 °C (pH 7.3) (RIFM, 2015c)

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6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00135 mm Hg (EPI Suite v4.11), 0.47, 0.60, and 1.99 hPa at 20, 25, and 50 °C, respectively (RIFM, 2015a)
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:** Not Available

3. Volume of use (worldwide band)

1 1–10 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:** 0.96% (RIFM, 2023)
2. **Inhalation Exposure*:** 0.00040 mg/kg/day or 0.027 mg/day (RIFM, 2023)
3. **Total Systemic Exposure**:** 0.014 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, 2017; Safford et al., 2015, 2017, 2024).

**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, 2017; Safford et al., 2015, 2017, 2024).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer classification: Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.6 (OECD, 2023)
I	I	I

6.2. Analogs selected

a. Genotoxicity: None
b. Repeated Dose Toxicity: β-Methylphenethyl alcohol (CAS # 1123-85-9)
c. Reproductive Toxicity: 3-Phenyl-1-propanol (CAS # 122-97-4)
d. Skin Sensitization: 2-Methyl-5-phenylpentanol (CAS # 25634-93-9)
e. Photoirritation/Photoallergenicity: None
f. Local Respiratory Toxicity: Phenethyl alcohol (CAS # 60-12-8)
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

2,2-Dimethyl-3-phenylpropanol 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, 2016); accessed on 10/17/23.

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, 2,2-dimethyl-3-phenylpropanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2,2-dimethyl-3-phenylpropanol 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 pre-incubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 2,2-dimethyl-3-phenylpropanol 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, 2008a). Under the conditions of the study, 2,2-dimethyl-3-phenylpropanol was not mutagenic in the Ames test.

The clastogenicity of 2,2-dimethyl-3-phenylpropanol 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 2,2-dimethyl-3-phenylpropanol in DMSO at concentrations up to 1650.0 μg/mL in the dose range finding study; the main study was conducted at concentrations up to 1650.0 μg/mL in the presence or absence of S9. Statistically significant increases (1.0%, 1.5%, 2.5% aberrant cells) in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed in the presence of S9 (RIFM, 2008b). However, these values were within the historical control range (0.0%–4.0% aberrant cells). Therefore, these increases were considered to be biologically irrelevant. Under the conditions of the study, 2,2-dimethyl-3-phenylpropanol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, 2,2-dimethyl-3-phenylpropanol does not present a concern for genotoxic potential.

Additional References: RIFM, 2008c.

Literature Search and Risk Assessment Completed On: 11/17/23.

11.1.2. Repeated dose toxicity

The MOE for 2,2-dimethyl-3-phenylpropanol 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 2,2-dimethyl-3-phenylpropanol. Read-across material β-methyl-phenethyl alcohol (CAS # 1123-85-9; see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

In a 13-week subchronic study, groups of 15 Wistar rats/sex/dose were administered β-methylphenethyl alcohol via the diet at doses of 0, 10, 40, or 160 mg/kg/day. Parameters that were tested included mortality, clinical signs, body weights, food and water consumption, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, and histopathology. There was no treatment-related mortality throughout the study period. There was a significant decrease (7%–9%) in terminal body weights among treated females when compared to the controls, which was not dose-related and not observed in males. Thus, this was not considered to be a treatment-related adverse effect. There were no treatment-related effects on food intake, water intake, hematology, serum chemistry, semi-quantitative analysis of urine, renal concentration and dilution tests, or histology. Increased liver weights at the highest dose level in both sexes and increased kidney weights at the 2 highest doses in males were considered to be related to treatment. However, the significance of such alterations remained unknown in the absence of related histopathological alterations. It was concluded that the NOAEL in this study was 40 mg/kg/day (Gaunt et al., 1982).

Therefore, the 2,2-dimethyl-3-phenylpropanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the β-methylphenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to 2,2-dimethyl-3-phenylpropanol, 40/0.014 or 2857.

Additionally, the total systemic exposure to 2,2-dimethyl-3-phenylpropanol (14 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: 10/26/23.

11.1.3. Reproductive toxicity

The MOE for 2,2-dimethyl-3-phenylpropanol 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 2,2-dimethyl-3-phenylpropanol. Read-across material 3-phenyl-1-propanol (CAS # 122-97-4; see Section VI) has sufficient data to support the reproductive toxicity endpoint.

In a GLP- and OECD 422-compliant study, 12 Sprague Dawley rats/sex/dose were administered 3-phenyl-1-propanol via gavage at doses of 0, 100, 300, and 1000 mg/kg/day. Males were treated for 2 weeks premating through until sacrifice (at least 50 days); females were treated for 2 weeks before mating through lactation day (LD) 13. An additional 12 Sprague Dawley rats/sex/dose at 0 and 1000 mg/kg/day were maintained as recovery groups for 2 weeks after treatment. No treatment-related effects were observed in the estrous cycle, precoital time, or fertility data. No effects were seen in pup anogenital distance or nipple retention. Decreases in pup survival, viability index, and body weight were observed at the high dose. Based on no adverse effects seen in parental animals up to the highest dose, the fertility NOAEL for this study was determined to be 1000 mg/kg/day. Based on mortality and decreased body weights of pups at the high dose, the developmental toxicity NOAEL was determined to be 300 mg/kg/day (RIFM, 2016).

Therefore, the 2,2-dimethyl-3-phenylpropanol MOE for the developmental toxicity endpoint can be calculated by dividing the 3-phenyl-1-propanol NOAEL in mg/kg/day by the total systemic exposure to 2,2-dimethyl-3-phenylpropanol, 300/0.014, or 21429.

The 2,2-dimethyl-3-phenylpropanol MOE for the fertility endpoint can be calculated by dividing the 3-phenyl-1-propanol NOAEL in mg/kg/day by the total systemic exposure to 2,2-dimethyl-3-phenylpropanol, 1000/0.014, or 71429.

Additionally, the total systemic exposure to 2,2-dimethyl-3-phenylpropanol (14 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: 10/26/23.

11.1.4. Skin sensitization

Based on the existing data on the target material and read-across material 2-methyl-5-phenylpentanol, 2,2-dimethyl-3-phenylpropanol presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for 2,2-dimethyl-3-phenylpropanol. Therefore, 2-methyl-5-phenylpentanol (CAS # 25634-93-9; see Section VI) was used for the risk assessment of 2,2-dimethyl-3-phenylpropanol. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, 2,2-dimethyl-3-phenylpropanol is not considered a skin sensitizer. 2,2-Dimethyl-3-phenylpropanol and read-across material 2-methyl-5-phenylpentanol are predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.6). In a guinea pig maximization test, read-across material 2-methyl-5-phenylpentanol did not lead to skin sensitization reactions (RIFM, 1988). A guinea pig Buehler test with 2,2-dimethyl-3-phenylpropanol did not present reactions indicative of sensitization (RIFM, 1981a). Additionally, in a Confirmation of No Induction in Humans (CNIH) test with 10% (patch size unknown) of read-across material 2-methyl-5-phenylpentanol in 1:1 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1997).

Based on the weight of evidence (WoE) from structural analysis, animal studies, and a human study on the read-across material as well as the target material, 2,2-dimethyl-3-phenylpropanol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/14/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra and limited data, 2,2-dimethyl-3-phenylpropanol would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. 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). No evidence for photoirritation or photoallergy was observed in guinea pigs at the maximum tested concentration of 10% and 20% (RIFM, 1982a; RIFM, 1982b; RIFM, 1981b). However, the irradiation doses used in these studies were likely not sufficient, and appropriate controls were not included. Based on the lack of absorbance, 2,2-dimethyl-3-phenylpropanol does not present a concern for photoirritation or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/31/23.

11.1.6. Local respiratory toxicity

There are no inhalation data available on 2,2-dimethyl-3-phenylpropanol; however, in an acute, 2-week inhalation study for the analog phenethyl alcohol (CAS # 60-12-8; see Section VI), a NOAEC of 5 mg/m^3 was reported (RIFM, 2013).

Table 1
Summary of existing data on 2-methyl-5-phenylpentanol as a read-across for 2,2-dimethyl-3-phenylpropanol.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction)	NOEL-HMT (induction) µg/cm²	LOEL (induction) µg/cm²	WoE NESIL µg/cm²	LLNA Weighted Mean EC3 Value µg/cm²	GPMT[2]	Buehler
No evidence of sensitization[3]	10% (patch size unknown)	N/A	N/A	N/A	N/A	Negative	N/A
	In vitro Data				*In silico* protein binding alerts (OECD Toolbox v4.6)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	N/A	N/A	N/A		No alert found	No alert found	Schiff base formation

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; EC3 = concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = Not Available.
[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
[2]Studies conducted according to the OECD TG 406 are included in the table.
[3]Determined based on Criteria for the RIFM safety evaluation process for fragrance ingredients (Api et al., 2015).

11.1.6.1. Risk assessment. The calculated chronic inhalation exposure was considered along with toxicological data from the scientific literature to estimate the MOE when used in perfumery. In a 2-week acute inhalation study conducted in rats, a NOAEC of 5.0 mg/m^3 was reported for phenethyl alcohol (RIFM, 2013). Phenethyl alcohol was administered by nose-only inhalation exposure to male and female Sprague Dawley rats (10 per sex per group) at 0.5, 5.0, and 50 mg/m^3 (equivalent to 0.1, 1, and 10 ppm) for 2 weeks (6 h/day, 5 days/week) for a total of 10 exposures. Test material-related effects were limited to mononuclear infiltrates in the liver, and histiocytic infiltrates in the lungs of the 50 mg/m^3 group females, and non-adverse microscopic findings in the nasal cavity at 0.5, 5.0, and 50 mg/m^3.

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

- (5.0 mg/m^3) × (1 m^3/1000 L) = 0.0050 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/day
- (0.0050 mg/L) × (61.2 L/d) = 0.306 mg/day
- (0.306 mg/day)/(0.0016 kg lung weight of rat**) = 191.3 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.027 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; 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 0.042 mg/kg lung weight/day, resulting in a MOE of 4554.8 (i.e., [191.3 mg/kg lung weight/-day]/[0.042 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.027 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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Additional References: None.
Literature Search and Risk Assessment Completed On: 11/13/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,2-dimethyl-3-phenylpropanol 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, 2,2-dimethyl-3-phenylpropanol 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 2,2-dimethyl-3-phenylpropanol 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 I.

11.2.2. Risk assessment

Based on the current VoU (2019), 2,2-dimethyl-3-phenylpropanol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 1995:** The biodegradability of 2, 2-dimethyl-3-phenylpropanol was determined in a BOD (biochemical oxygen demand) test for insoluble substances (BODIS). A defined mineral solution was inoculated with a mixed bacterial inoculum stabilized under laboratory conditions for one week and then spiked with 2, 2-dimethyl-3-phenylpropanol. The degradation was followed by weekly measurements of the BOD in the aqueous phase for a 28-day period. The average degradation rate of 2,2-dimethyl-3-phenylpropanol was 15.28% at the end of the test.

RIFM, 2022: Ready biodegradability of the test material was evaluated according to the OECD 301F method. Under the conditions of the study, biodegradation of 12% was observed after 60 days.

11.2.2.1.2. Ecotoxicity. **RIFM, 2000:** A 48-h *Daphnia magna* acute immobilization test was conducted with 2,2-dimethyl-3-phenylpropanol. Nominal test concentrations were 4.3, 9.4, 20.7, 45.5, or 100 mg/L. The calculated EC50 value at 48 h was 43 mg/L.

11.2.2.1.3. Other available data. 2,2-Dimethyl-3-phenylpropanol has been registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Since 2,2-dimethyl-3-phenylpropanol has passed the screening criteria, measured data are included for completeness only and have not been used for PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>34.33</u>			1000000	0.0343	

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	<1	<1
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 0.00343 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the

current reported VoU.

Literature Search and Risk Assessment Completed On: 11/13/23.

Literature search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 07/22/24.

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.2024.114975.

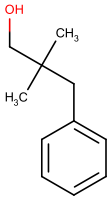
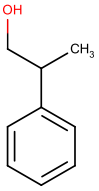
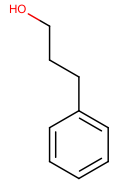
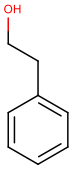
Appendix

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 v4.6 (OECD, 2023).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.6 (OECD, 2023).
- 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 v4.6 (OECD, 2023).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.6 (OECD, 2023).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.6 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	2,2-Dimethyl-3-phenylpropanol	2-Methyl-5-phenylpentanol	β-Methylphenethyl alcohol	3-Phenyl-1-propanol	Phenethyl alcohol
CAS No.	13351-61-6	25634-93-9	1123-85-9	122-97-4	60-12-8
Structure					
Similarity (Tanimoto Score)		0.67	0.59	0.89	0.59
SMILES	CC(C)(CO)Cc1ccccc1	CC(CO)CCCc1ccccc1	CC(CO)c1ccccc1	OCCCc1ccccc1	OCCc1ccccc1
Endpoint		Skin sensitization	Repeated dose toxicity	Reproductive toxicity	Local respiratory toxicity
Molecular Formula	$C_{11}H_{16}O$	$C_{12}H_{18}O$	$C_9H_{12}O$	$C_9H_{12}O$	$C_8H_{10}O$
Molecular Weight (g/mol)	164.248	178.275	136.194	136.194	122.167
Melting Point (°C, EPI Suite)	34.50	37.93	−13.00	16.79	−27.00
Boiling Point (°C, EPI Suite)	260.56	283.33	232.23	235.00	218.20
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.80E-01	3.99E-02	2.53E+00	2.65E+00	1.16E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	6.68E+02	2.03E+02	5.68E+03	5.68E+03	2.22E+04
Log KOW	2.93	3.46	1.98	1.88	1.36
J_{max} (μg/cm^2/h, SAM)	40.02	16.95	170.24	146.17	355.17
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	6.84E-02	9.08E-02	3.88E-02	2.06E-02	2.59E-02
Repeated Dose Toxicity					
Repeated Dose (HESS)	Chlorphentermine (Hepatotoxicity) Alert|Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert		Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert		
Reproductive Toxicity					
ER Binding (OECD QSAR Toolbox v4.6)	Non-binder, without OH or NH_2 group			Non-binder, without OH or NH_2 group	
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)			Toxicant (good reliability)	
Skin Sensitization					
Protein Binding (OASIS v1.1)	No alert found	No alert found			
Protein Binding (OECD)	No alert found	No alert found			
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)			
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found			
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified	No skin sensitization reactivity domain alerts identified			
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.6)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on the 2,2-dimethyl-3-phenylpropanol (CAS # 13351-61-6). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 2-methyl-5-phenylpentanol (CAS # 25634-93-9), β-methylphenethyl alcohol (CAS # 1123-85-9), 3-phenyl-1-propanol (CAS # 122-97-4), and phenethyl alcohol (CAS # 60-12-8) were identified as read-across materials with data for their respective toxicological endpoints.

Conclusions

- 2-Methyl-5-phenylpentanol (CAS # 25634-93-9) was used as a read-across analog for the target material, 2,2-dimethyl-3-phenylpropanol (CAS # 13351-61-6), for the skin sensitization endpoint.
  - o The target material and the read-across analogs are structurally similar and belong to the structural class of primary aryl alcohols.

- The key difference between the target material and the read-across analogs is the length of the carbon chain between the primary alcohol and aromatic ring. The target material has a shorter chain with 2 methyl substituents, and the read-across analog has a longer chain with one methyl substituent. This structural difference is toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analogs are sufficiently similar to enable comparison of their toxicological properties.
- 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.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.6, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- Neither the target nor the read-across analog have 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* i*n silico* alerts is consistent with the data.
- 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.

- β-Methylphenethyl alcohol (CAS # 1123-85-9) was used as a read-across analog for the target material, 2,2-dimethyl-3-phenylpropanol (CAS # 13351-61-6), for the repeated dose toxicity endpoint.
  - The target material and the read-across analogs are structurally similar and belong to the structural class of primary aryl alcohols.
  - The key difference between the target material and the read-across analogs is the length of the carbon chain between the primary alcohol and aromatic ring. The target material has a longer chain with 2 methyl substituents, and the read-across analog has a shorter chain with one methyl substituent. This structural difference is toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.6, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and the read-across analog have renal toxicity alerts. The target material also has a hepatotoxicity alert. 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* alerts and predictions are superseded by the data.
  - 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.
- 3-Phenyl-1-propanol (CAS # 122-97-4) was used as a read-across analog for the target material, 2,2-dimethyl-3-phenylpropanol (CAS # 13351-61-6), for the reproductive toxicity endpoint.
  - The target material and the read-across analogs are structurally similar and belong to the structural class of primary aryl alcohols.
  - The key difference between the target material and the read-across analogs is the number of methyl substituents in the carbon chain between the primary alcohol and aromatic ring. The target material has 2 methyl substituents, and the read-across analog has no methyl substituent. This structural difference is toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.6, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and the read-across analog are non-binders by OECD QSAR Toolbox v4.6 and are toxicants by CAESAR v2.1.6 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 *in silico* alerts and predictions are superseded by the data.
  - 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.
- Phenethyl alcohol (CAS # 60-12-8) was used as a read-across analog for the target material, 2,2-dimethyl-3-phenylpropanol (CAS # 13351-61-6), for the local respiratory toxicity endpoint.
  - The target material and the read-across analogs are structurally similar and belong to the structural class of primary aryl alcohols.
  - The key difference between the target material and the read-across analogs is the length of the carbon chain between the primary alcohol and aromatic ring. The target material has a longer chain with 2 methyl substituents, and the read-across analog has a shorter chain with no methyl substituent. This structural difference is toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - 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.

- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.6, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- Neither the target nor the read-across analog has alerts for local respiratory toxicity. The data on the read-across analog confirms that the material does not pose a concern for local respiratory 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 is consistent with the data.
- 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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