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RIFM fragrance ingredient safety assessment, 3-phenyl-1-propanol, CAS Registry Number 122-97-4

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

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

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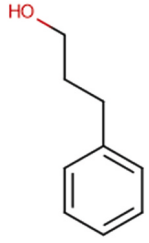

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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

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

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Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

3-Phenyl-1-propanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3-phenyl-1-propanol is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog benzyl alcohol (CAS # 100-51-6) provided 3-phenyl-1-propanol a No Expected Sensitization Induction Level (NESIL) of 5900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 3-phenyl-1-propanol is not expected to be phototoxic/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; 3-phenyl-1-propanol 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 in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2002b; RIFM, 2018)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(RIFM, 2016e)
Reproductive Toxicity: Developmental NOAEL = 300 mg/kg/day. Fertility NOAEL = 1000 mg/kg/day.	(RIFM, 2016e)
Skin Sensitization: NESIL = 5900 μg/cm^2.	RIFM (2005b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 5.0 mg/m^3.	RIFM (2013b)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical Measured Value: 83% (OECD 301F)	RIFM (2013c)
Bioaccumulation:	
Screening-level: 4.486 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-h Algae EC50: 43.164 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 43.164 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 4.3164 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1	

1. Identification

1. **Chemical Name:** 3-Phenyl-1-propanol
2. **CAS Registry Number:** 122-97-4
3. **Synonyms:** Benzenepropanol; Benzylethyl alcohol; Dihydrocinnamyl alcohol; Hydrocinnamyl alcohol; Phenethyl carbinol; Phenylpropyl alcohol; 3-Phenylpropyl alcohol; フェニルアルキル (C = 3–5)アルコール; 3-Phenylpropan-1-ol; Phenylpropylalkohol; 3-Phenyl-1-propanol
4. **Molecular Formula:** $C_9H_{12}O$
5. **Molecular Weight:** 136.19 g/mol
6. **RIFM Number:** 249
7. **Stereochemistry:** Isomer not specified. Stereocenter not present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 235 °C (Fragrance Materials Association [FMA]), 243.15 °C (EPI Suite), 236–238 °C at 1013 hPa (RIFM, 2015c)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA), 116.5 °C (corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015d)
3. **Log K_{OW}:** 1.6 (RIFM, 2013d), 2.06 (EPI Suite)
4. **Melting Point**: 16.79 °C (EPI Suite), no melting point down to −100 °C at 1024 hPa (RIFM, 2015c)
5. **Water Solubility:** 6969 mg/L (EPI Suite)
6. **Specific Gravity:** 0.998–1.002 (FMA), 1.000–1.004 (FMA)
7. **Vapor Pressure:** 0.005 mm Hg at 20 °C (EPI Suite v4.0), 0.03 mm Hg at 20 °C (FMA), 0.00848 mm Hg at 25 °C (EPI Suite)
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 to very pale yellow, slightly oily, slightly viscous liquid with a sweet hyacinth-mignonette odor

3. Volume of use (Worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.087% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00039 mg/kg/day or 0.030 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0023 mg/kg/day (RIFM, 2019)

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

5. Derivation of systemic absorption

1. **Dermal:** 77%, read-across from phenethyl alcohol (CAS # 60-12-8)

RIFM, 2013a (data also available in RIFM, 1986; RIFM, 1987; RIFM, 1988a; RIFM, 1988b; RIFM, 1990; Ford et al., 1987; Ford, 1990): Studies were conducted to compare the dermal absorption, plasma pharmacokinetics, and excretion of phenylethyl alcohol (PEA) by pregnant and non-pregnant rats, non-pregnant rabbits, and non-pregnant humans. Following dermal (430, 700, or 1400 mg/kg), gavage (430 mg/kg), or dietary (430 mg/kg) administration of PEA to rats, plasma concentrations of PEA were found to be low regardless of the route of administration. The plasma concentrations of phenylacetic acid (PAA, the major metabolite of PEA) greatly exceeded the concentrations of PEA and were highest after gavage, followed by dermal then dietary administration. The pharmacokinetic parameters were compared following topical application of [14]C-labeled PEA to rats, rabbits, and humans (specific activities of dosing solutions: 58–580, 164, and 50 μCi/mL, respectively). In rabbits, the plasma concentration-time profile for PAA was markedly prolonged compared to rats or humans. In humans, only 7.6% of the applied dose of PEA was absorbed, versus 77% in rats and 50% in rabbits. Conservatively, the rat absorption data was selected for this safety assessment due to poor recovery of radioactivity due to evaporation from the human study (87.4% in rats compared to 10.8% in humans).

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Benzyl alcohol (CAS # 100-51-6)
   e. **Phototoxicity/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

3-Phenyl-1-propanol is reported to occur in the following foods by the VCF*:

Artocarpus species.
Capers (*Capparis spinoza*).
Cloudberry (*Rubus chamaemorus* L.)
Guava and Feyoa
Honey.
Melon.
Passion fruit (*Passiflora species*).
Sapodilla fruit (*Achras sapota* L.)
Strawberry.
Vaccinium species.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. This is a partial list.

9. REACH dossier

Available; accessed on 12/09/21 (ECHA, 2016).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 3-phenyl-1-propanol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.45
2	Products applied to the axillae	0.14
3	Products applied to the face/body using fingertips	2.7
4	Products related to fine fragrances	2.5
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.64
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.64
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.64
5D	Baby cream, oil, talc	0.21
6	Products with oral and lip exposure	1.5
7	Products applied to the hair with some hand contact	1.0
8	Products with significant ano-genital exposure (tampon)	0.21
9		4.9

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Products with body and hand exposure, primarily rinse-off (bar soap)	
10A	Household care products with mostly hand contact (hand dishwashing detergent)	6.2
10B	Aerosol air freshener	18
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.21
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 3-phenyl-1-propanol, the basis was the reference dose of 3.0 mg/kg/day, a skin absorption value of 77%, and a skin sensitization NESIL of 5900 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 3-phenyl-1-propanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 3-phenyl-1-propanol 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 3-phenyl-1-propanol 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, 2002c). Under the conditions of the study, 3-phenyl-1-propanol was not mutagenic in the Ames test.

The clastogenic activity of 3-phenyl-1-propanol 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 3-phenyl-1-propanol in DMSO at concentrations up to 1362 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1362 μg/mL in the presence and absence of metabolic activation. 3-phenyl-1-propanol did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2018). Under the conditions of the study, 3-phenyl-1-propanol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 3-phenyl-1-propanol does not present a concern for genotoxic potential.

Additional References: 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; RIFM, 2017b.

Literature Search and Risk Assessment Completed On: 04/23/21.

11.1.2. Repeated dose toxicity

The MOE for 3-phenyl-1-propanol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 3-phenyl-1-propanol. 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 pre-mating through until sacrifice (at least 50 days); females were treated for 2 weeks-premating through to 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 mortality occurred throughout the study period. No treatment-related effects were observed on body weight, food consumption, functional behavior, motor activity, macroscopic, or microscopic findings. Total red blood cell (RBC) count was decreased in males at the high dose. Blood urea nitrogen (BUN) was decreased in males at the high dose. Glucose was increased in the serum of females at the mid and high doses. Total bilirubin, calcium, and inorganic phosphorus levels were increased in females at the high dose. Absolute and relative liver weights were increased in females at the high dose. Although these changes were statistically significant, they were not considered adverse due to the lack of correlated microscopic findings. Based on no toxicologically relevant adverse effects seen up to the highest dose, the NOAEL for this study was considered to be 1000 mg/kg/day (RIFM, 2016e).

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

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

Therefore, the 3-phenyl-1-propanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3-phenyl-1-propanol NOAEL in mg/kg/day by the total systemic exposure to 3-phenyl-1-propanol, 333/0.0023, or 144782.

Before and after correcting for skin absorption, the total systemic exposure to 3-phenyl-1-propanol (2.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/09/21.

11.1.3. Reproductive toxicity

The MOE for 3-phenyl-1-propanol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 3-phenyl-1-propanol. 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 pre-mating through until sacrifice (at least 50 days); females were treated for 2 weeks-premating through to 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 NOAEL was determined to be 300 mg/kg/day (RIFM,

2016e).

Therefore, the 3-phenyl-1-propanol 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 3-phenyl-1-propanol, 300/0.0023, or 130434.

The 3-phenyl-1-propanol 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 3-phenyl-1-propanol, 1000/0.0023, or 434782.

After correcting for skin absorption, the total systemic exposure to 3-phenyl-1-propanol (2.3 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.

11.1.3.2. Derivation of reference dose (RfD). Section secX provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and an RfD of 3 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for inter-species (10 ×) and intraspecies (10 ×) differences. The RfD for 3-phenyl-1-propanol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 300 mg/kg/day by the uncertainty factor, 100 = 3 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/09/21.

11.1.4. Skin sensitization

Based on the existing data and read-across to benzyl alcohol (CAS # 100-51-6), 3-phenyl-1-propanol is considered a skin sensitizer with a defined NESIL of 5900 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 3-phenyl-1-propanol. Based on the existing data and read-across material benzyl alcohol (CAS # 100-51-6; see Section VI), 3-phenyl-1-propanol is considered a skin sensitizer. The chemical structure of these materials indicates that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 3-Phenyl-1-propanol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens assay (RIFM, 2016c; ECHA, 2016). The read-across material, benzyl alcohol, was found to be negative in an *in vitro* DPRA, both positive and negative in KeratinoSens, positive in human cell line activation test (h-CLAT), and negative in U-SENS (RIFM, 2014; RIFM, 2015a; RIFM, 2015b; Urbisch, 2015; Piroird et al., 2015). In a murine local lymph node assay (LLNA), read-across material benzyl alcohol was not found to be sensitizing when tested up to 50% (12500 μg/cm^2) (RIFM, 2005a). In human maximization tests, no skin sensitization reactions were observed with 8% (5520 μg/cm^2) 3-phenyl-1-propanol in petrolatum or read-across material benzyl alcohol at 10% (6900 μg/cm^2) in petrolatum (RIFM, 1976; RIFM, 1979; RIFM, 1970). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 4% (444 μg/cm^2) 3-phenyl-1-propanol in petrolatum, no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1971). In CNIH tests with 23622 μg/cm^2, 17717 μg/cm^2, and 8858 μg/cm^2 of read-across material benzyl alcohol in 3:1 diethyl phthalate:ethanol (DEP:EtOH), reactions indicative of sensitization were observed in 2/56, 4/46, and 1/110 volunteers, respectively (RIFM, 2002a; RIFM, 2003; RIFM, 2004a). However, in 2 other CNIHs with 3543 μg/cm^2 and 5906 μg/cm^2 of read-across material benzyl alcohol in 3:1 DEP:EtOH, no reactions indicative skin sensitization induction were observed in 110 and 99 volunteers, respectively (RIFM, 2004b; RIFM, 2005b).

Based on the weight of evidence (WoE) from structural analysis, human studies, and data on the read-across material benzyl alcohol, 3-phenyl-1-propanol is a sensitizer with a WoE NESIL of 5900 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and an RfD of 3 mg/kg/day.

Additional References: Natsch (2007); Natsch (2008); Emter et al., 2010; Natsch (2013); Alepee et al., 2015; McKim et al., 2010; RIFM, 2017a; Sharp (1978); Klecak et al., 1977; Ishihara et al., 1986; Hausen et al., 1992; Kashima et al., 1993a; Hausen et al., 1995; Kashima et al., 1993b.

Literature Search and Risk Assessment Completed On: 04/23/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 3-phenyl-1-propanol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 3-phenyl-1-propanol 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 phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 3-phenyl-1-propanol does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/13/21.

11.1.6. Local respiratory toxicity

There are no inhalation data available on 3-phenyl-1-propanol; however, in an acute, 2-week inhalation study for the read-across analog phenethyl alcohol (CAS # 60-12-8; see Section VI), a NOAEC of 5.0 mg/m^3 was reported (RIFM, 2013b).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2-week acute inhalation study conducted

Table 1
Data summary for benzyl alcohol as read-across material for 3-phenyl-1-propanol.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human 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
>12500 [1]	NA	5906	6900	8858	5900

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

in rats at doses of 0.5, 5.0, and 50 mg/m^3, a NOAEC of 5.0 mg/m^3 was reported for phenethyl alcohol (RIFM, 2013b). 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 0.030 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford, 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 0.046 mg/kg lung weight/day resulting in a MOE of 4158.7 (i.e., [191.3 mg/kg lung weight/-day]/[0.046 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.030 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

Additional References: Carpenter et al., 1974; RIFM, 1974; Goodrich et al., 1981; RIFM, 1980; Price (1977); Rumyantsev et al., 1987; UGCM, 1997; Buchbauer et al., 1993; Gilbert and Kemp, 1996; Sakuma et al., 1997; Dalton et al., 1997; Silver (1992); Doty (1994); Buchbauer et al., 1992; Caccappolo et al., 2000; Smeets and Dalton, 2002

Literature Search and Risk Assessment Completed On: 04/16/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3-phenyl-1-propanol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3-phenyl-1-propanol 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 not identify 3-phenyl-1-propanol as possibly 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, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 3-phenyl-1-propanol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. **RIFM, 2013c:** The purpose of this study was to determine the ready biodegradability of the test material using the manometric respirometry test according to the OECD 301F method. The test material underwent 83% biodegradation after 28 days in the test conditions.

11.2.3.2. Ecotoxicity. **RIFM, 2016a:** A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50, based on nominal concentrations, was reported to be 60.6 mg/L.

RIFM, 2016b: An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 values based on nominal test concentrations for growth rate and yield were reported to be 109 mg/L and 100 mg/L, respectively.

RIFM, 2016d: A fish (zebrafish) acute toxicity study was conducted according to the OECD 203 method under static conditions. The 72-h LC50 based on nominal test concentration (verified by HPLC and DOC) was reported to be greater than 61 mg/L.

11.2.3.3. Other available data. 3-Phenyl-1-**propanol** has been registered under REACH, with no additional data available at this time.

11.2.3.3.1. Risk assessment refinement. Since 3-phenyl-1-propanol 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	1.6	1.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	409			1000000	0.409	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	99.298	56.683	43.164	10000	4.3164	Neutral Organics

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

The RIFM PNEC is 4.3164 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: 03/29/21.

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
- **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 HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **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 12/09/21.

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 F. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2022.113009.

Appendix

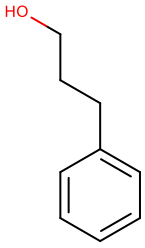
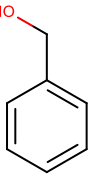
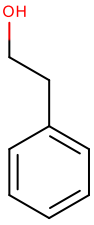
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- 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 v4.11 (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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018) and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	3-phenyl-1-propanol; 3-phenylpropanol; benzenepropanol; 3-phenylpropan-1-ol; 3-phenylpropanol-1; 1-propanol, 3-phenyl-	Benzyl alcohol	Phenethyl alcohol
CAS No.	122-97-4	100-51-6	60-12-8
Structure			
Similarity (Tanimoto Score)		0.47	0.65
SMILES	OCCCc1ccccc1	OCc1ccccc1	OCCc1ccccc1
Endpoint		Skin sensitization	Local respiratory toxicity
Molecular Formula	$C_9H_{12}O$	C_7H_8O	$C_8H_{10}O$
Molecular Weight (g/mol)	136.194	108.14	122.167
Melting Point (°C, EPI Suite)	16.79	−15.50	−27.00
Boiling Point (°C, EPI Suite)	235.00	205.30	218.20
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.65E+00	1.25E+01	1.16E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.68E+03	4.29E+04	2.22E+04
Log K_{OW}	1.88	1.1	1.36
J_{max} (μg/cm^2/h, SAM)	146.17	643.34	355.17
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.06E-02	3.41E-02	2.59E-02
Skin Sensitization			
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
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 domains alerts identified.	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on the target material, 3-phenyl-1-propanol (CAS # 122-97-4). Hence, *in silico* evaluation was conducted by determining a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, benzyl alcohol (CAS # 100-51-6) and phenethyl alcohol (CAS # 60-12-8) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusion

- Benzyl alcohol (CAS # 100-51-6) was used as a read-across analog for the target material 3-phenyl-1-propanol (CAS # 122-97-4) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of primary aryl alcohols.
  - o The target material and the read-across analog share a phenethyl fragment.
  - o The key difference between the target material and the read-across analog is that the target material has a 1-carbon longer chain between the primary alcohol and the aromatic moiety. The read-across analog contains the structural features of the target material that are relevant to this

endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - 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.
  - There are no *in silico* alerts for skin sensitization which is consistent with 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 # 60-12-18) was used as a read-across analog for the target material 3-phenyl-1-propanol (CAS # 122-97-4) for the local respiratory toxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the structural class of primary aryl alcohols.
  - The target material and the read-across analog share a phenethyl fragment.
  - The key difference between the target material and the read-across analog is that the target material has a 1-carbon longer chain between the primary alcohol and the aromatic moiety. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - 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.
  - There is no *in silico* alert for the local respiratory toxicity endpoint, which 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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