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Short Review

RIFM fragrance ingredient safety assessment, 3-phenylpropionic acid, CAS Registry Number 501-52-0

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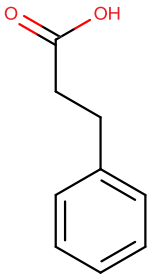
Version: 112018. This version replaces any previous versions.

Name: 3-Phenylpropionic acid

CAS Registry Number: 501-52-0



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
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable 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

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PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
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-Phenylpropionic acid was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs phenylacetic acid (CAS # 103-82-2) and 2-hydroxyphenylacetic acid (CAS # 614-75-5) and weight of evidence from benzoic acid (CAS # 65-85-0) show that 3-phenylpropionic acid is not expected to be genotoxic. Data on read-across analog phenylacetic acid (CAS # 103-82-2) provide a calculated MOE > 100 for the developmental toxicity endpoint. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material; exposure is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog phenylacetic acid (CAS # 103-82-2) show there are no safety concerns for 3-phenylpropionic acid for skin sensitization under current declared use levels. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 3-phenylpropionic acid is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-phenylpropionic acid was found not to be PBT per the IFRA Environmental Standards; its risk quotients, based on current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 1983a; RIFM, 1982; RIFM, 1993)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity:
Developmental toxicity NOAEL = 500 mg/kg/day. US EPA (2005)
Reproductive toxicity NOAEL unavailable; exposure is below the TTC.
Skin Sensitization: Not sensitizing. (RIFM, 1965; RIFM, 1972)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 3.17 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 3.16 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 113.3 - mg/L (RIFM Framework; 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 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 113.3 - mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.1133 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 3-Phenylpropionic acid
2. **CAS Registry Number:** 501-52-0
3. **Synonyms:** Benzenepropanoic acid; Benzylacetic acid; Dihydrocinnamic acid; Hydrocinnamic acid; β-Phenylpropionic acid; 3-Phenylpropanoic acid; 3-Phenylpropionic acid
4. **Molecular Formula:** $C_9H_{10}O_2$
5. **Molecular Weight:** 150.18
6. **RIFM Number:** 6779

2. Physical data

1. **Boiling Point:** 282.74 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.29 (EPI Suite)
4. **Melting Point**: 217 °C (FMA Database), 69.3 °C (EPI Suite)
5. **Water Solubility:** 5046 mg/L (EPI Suite)
6. **Specific Gravity:** 1.07100 @ 25.00 °C*
7. **Vapor Pressure:** 0.000473 mm Hg @ 20 °C (EPI Suite v4.0), 0.002 mm Hg 20 °C (FMA Database), 0.00089 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** White crystals with a medium floral, sweet, fatty, rose, musk, cinnamon odor at 1% in dipropylene glycol*

*http://www.thegoodscentscompany.com/data/rw1020511.html, retrieved on 4/9/2015.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.036% (RIFM, 2014b)
3. **Inhalation Exposure*:** 0.000070 mg/kg/day or 0.0049 mg/day (RIFM, 2014b)
4. **Total Systemic Exposure **:** 0.00063 mg/kg/day (RIFM, 2014b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%

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

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. **Analogs Selected:**
   a. **Genotoxicity:** Phenylacetic acid (CAS # 103-82-2), 2-hydroxyphenylacetic acid (CAS # 614-75-5), benzoic acid (CAS # 65-85-0)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** Phenylacetic acid (CAS # 103-82-2)
   d. **Skin Sensitization:** Phenylacetic acid (CAS # 103-82-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification**: See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. Natural occurrence (discrete chemical) or composition (NCS)

3-Phenylpropionic acid is reported to occur in the following foods by the VCF*:

Beer.
Cheddar cheese.
Cheese, various types.
Cherimoya (*Annona cherimolia* Mill.)
Cinnamomum species.
Citrus fruits.
Cloudberry (*Rubus chamaemorus* L.)
Cocoa category.
Grape (*Vitis* species)
Grape brandy.
Guava and feyoa
Honey.
Licorice (*Glycyrrhiza glabra* L.)
Litchi (*Litchi chinensis* Sonn.)
Mangifera species.
Mushroom.
Papaya (*Carica papaya* L.)
Pear brandy.
Pumpkin seed oil.
Rambutan (*Nephelium lappaceum* L.)
Strawberry (*Fragaria* species)
Syzygium species.
Wine.

*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.

8. IFRA standard

None.

9. REACH dossier

Available; accessed 6/13/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 3-phenylpropionic acid does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 3-Phenylpropionic acid was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2014a). There are no data assessing the mutagenic activity of 3-phenylpropionic acid. The mutagenic activity of read-across material phenylacetic acid (CAS # 103-82-2; see Section V) was assessed in an Ames assay conducted equivalent to OECD TG 471 using the plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with phenylacetic acid in dimethyl sulfoxide (DMSO) at concentrations from 1 to 10000 μg/plate in the presence and absence of S9. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 1983a). Under the conditions of this study, phenylacetic acid was considered not mutagenic in the Ames test. A mammalian cell gene mutation assay was conducted on phenylacetic acid in compliance with GLP regulations and in accordance with guidelines similar to OECD TG 476. The potential of phenylacetic acid to induce mutations at the TK locus in mouse L5178Y TK ± lymphoma cells was evaluated. Mouse L5178Y TK ± lymphoma cells were treated with phenylacetic acid in DMSO at doses of 31.3–1000 μg/mL (with activation) or 31.3–1500 μg/mL (without activation) for 4 h. No significant increases in the frequency of mutant colonies were observed with any dose of phenylacetic acid, either in the presence or absence of S9 metabolic activation (RIFM, 1982). Under the conditions of the study, phenylacetic acid was considered not mutagenic in either the presence or absence of S9 metabolic activation.

There are no data assessing the clastogenic activity of 3-phenylpropionic acid. Read-across material 2-hydroxyphenylacetic acid (CAS # 614-75-5; see Section V) was assessed for clastogenic activity in an *in vitro* chromosome aberration assay using cultured Chinese hamster ovary K1 cells. The test was conducted in compliance with GLP regulations and used a protocol similar to OECD TG 473. Chinese hamster ovary cells were treated with 2-hydroxyphenylacetic acid in DMSO for 12 h at concentrations of 625, 1250, 2500, or 5000 μg/mL in the presence or absence of S9 metabolic activation (RIFM, 1993). Under the conditions of the study, 2-hydroxyphenylacetic acid was considered not clastogenic in either the presence or absence of S9 metabolic activation, and this can be extended to 3-phenylpropionic acid.

Data on read-across material benzoic acid (CAS # 65-85-05; see Section V) was also considered as weight of evidence for clastogenicity. The clastogenicity of benzoic acid was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations. Chinese hamster lung cells were treated with benzoic acid in DMSO at concentrations up to 1.5 mg/mL in the absence of exogenous metabolic activation. Slight increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed without S9 metabolic activation (Ishidate et al., 1984). Under the conditions of the study, benzoic acid was considered equivocal in the *in vitro* chromosome aberration assay. Additionally, this result was interpreted as

weakly mutagenic in an OECD SIDS assessment (OECD, 2001). There was no indication of a genotoxic response in tests with mammalian cells (chromosome aberrations in Chinese hamster lung and ovary cells, sister chromatid exchange in human lymphoblastoid cells, and human lymphocytes) without metabolic activation (Oikawa et al., 1980; Jansson et al., 1988). Benzoic acid significantly increased the chromosomal aberration, sister chromatid exchange, and micronucleus frequency without changing the pH of the medium in a dose-dependent manner. Benzoic acid did not show any genotoxic effects in an *in vivo* comet assay performed on tissues from the glandular stomach, colon, liver, kidney, urinary bladder, lung, brain, and bone marrow by oral administration of 1000 mg/kg benzoic acid for 3- and 24-h treatment periods (Sasaki et al., 2002). In another *in vitro* comet assay, benzoic acid was dissolved in water and tested up to 5 mM in human lymphocytes, and only at the highest concentration of benzoic acid increased both tail moment and percent tail DNA (Demir et al., 2010). However, no dose response was observed; hence, the biological relevance of the study is questionable. Since the sodium salt of benzoic acid, sodium benzoate, readily protonates to benzoic acid, studies with sodium benzoate are also representative for benzoic acid (OECD, 2001). In a cytogenetic assay, male rats were administered single or multiple gavage doses of 50, 500, or 5000 mg/kg of sodium benzoate. No significant increase in chromosomal aberrations in the bone marrow were observed. In a dominant lethal assay, male rats were administered sodium benzoate in single or multiple gavage doses of 50, 500, or 5000 mg/kg, and no mutagenic effects were observed (OECD, 2001). In addition, a lifelong study (average lifespan 2.5–3.5 years) using male and female Swiss Albino mice given 2% sodium benzoate continuously in drinking water concluded with no carcinogenic effect (OECD, 2001). Taken together, benzoic acid and sodium benzoate did not exhibit genotoxic effects *in vivo* and were negative in a long-term carcinogenicity study. Therefore, it can be concluded that benzoic acid does not present a concern for genetic toxicity, and this can be extended to 3-phenylpropionic acid.

Based on the available data, 3-phenylpropionic acid does not present a concern for genotoxic potential.

Additional References: RIFM, 1994a; RIFM, 1994b; Heck et al., 1989; ECHA, 2017)

Literature Search and Risk Assessment Completed On: 08/01/2018.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 3-phenylpropionic acid or any read-across materials. The exposure is below the TTC at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 3-phenylpropionic acid or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure for 3-phenylpropionic acid (0.63 μg/kg/day) is below the TTC (30 μg/kg/day) at the current level of use for the repeated dose toxicity endpoint.

Additional References: Schafer and Bowles, 1985; Hoshino (1940); RIFM, 1983b; Anderson et al., 1936; Boggs et al., 1963; Berthelot and Dieryck, 1939; Davies et al., 1956; Zaitsev and Rakhmanina, 1974; Sherwin and Kennard, 1919; Zaitsev and Rakhmanina, 1974; Burton et al., 1986.

Literature Search and Risk Assessment Completed On: 8/18/2015.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 3-phenylpropionic acid is adequate for the developmental toxicity endpoint at the current level of use.

There is insufficient reproductive toxicity data on 3-phenylpropionic acid or any read-across materials. The exposure is below the TTC at the current level of use.

10.1.3.1. Risk assessment. There are insufficient developmental or reproductive toxicity data on 3-phenylpropionic acid. In a reproductive/developmental toxicity screening assay on read-across material phenylacetic acid (CAS # 103-82-2; see Section V), 10 female Sprague Dawley rats/group received oral doses of 250, 500, or 1000 mg/kg/day of phenylacetic acid in corn oil for 1 week prior to a 7-day cohabitation period through gestation, parturition, and a 4-day postpartum period for a total of 39 days (US EPA, 2005). The NOAEL for female reproductive and developmental toxicity was 500 mg/kg/day. The NOAEL for maternal toxicity was 250 mg/kg/day. At 1000 mg/kg/day, a decrease in the mating index, pup viability, and body weight were observed. The study was conducted in compliance with GLP. There are no data on male reproductive toxicity data for 3-phenylpropionic acid or any of the read-across materials. **Therefore, the 3-phenylpropionic acid MOE for the developmental toxicity endpoint can be calculated by dividing the phenylacetic acid NOAEL by the total systemic exposure for 3-phenylpropionic acid, 500/0.00063, or 793651.**

In addition, the current total systemic exposure for 3-phenylpropionic acid (0.63 μg/kg/day) is below the TTC (30 μg/kg/day) for the developmental and reproductive toxicity endpoints at the current level of use.

Additional References: Kumar et al., 1989; Maganova and Saitsev, 1973; Zaitsev and Maganova, 1975; Dawson et al., 1996; Hamers et al., 1989.

Literature Search and Risk Assessment Completed On: 8/18/2015.

10.1.4. Skin sensitization

Based on existing data on read-across analog phenylacetic acid (CAS # 103-82-2), 3-phenylpropionic acid does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. The chemical structure indicates that this material is not expected to react with skin proteins (Toxtree 2.6.6, OECD toolbox v3.3). No human or animal sensitization data exist for 3-phenylpropionic acid. However, in guinea pig tests, read-across material phenylacetic acid did not exhibit the potential to induce skin sensitization (Klecak, 1985). In a human maximization test, no reactions indicative of sensitization were observed at the maximum tested concentration of 2% phenylacetic acid (1380 μg/cm2) in 25 volunteers (RIFM, 1972). In a human repeat insult patch test, 0.125% phenylacetic acid in alcohol SDA39C did not produce reactions indicative of sensitization in any of the subjects tested (RIFM, 1965).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/02/2016.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, 3-phenylpropionic acid would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 3-phenylpropionic acid in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, 3-phenylpropionic acid does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/26/16.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 3-phenylpropionic acid is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 3-phenylpropionic acid. Based on the Creme RIFM Model, the inhalation exposure is 0.0049 mg/day. This exposure is 286 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 8/1/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3-phenylpropionic acid 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-phenylpropionic acid 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 v4.1 (US EPA, 2012a) did not identify 3-phenylpropionic acid as either being possibly persistent nor 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), 3-phenylpropionic acid does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.3.3. Other available data. 3-Phenylpropionic acid has been registered for REACH and the following additional data is available:

A fish (*Danio rerio*) acute toxicity study was conducted according to the OECD 203 method under static conditions, and the 96-h LC50 based on nominal concentration was reported to be > 100 mg/L.

10.2.4. Risk assessment refinement

Since 3-Phenylpropionic acid has passed the screening criteria, measured data is included for completeness only and has 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	113.3			1,000,000	0.1133	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.29	2.29
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQ for this material is < 1. No further

assessment is necessary.

The RIFM PNEC is 0.1133 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 6/28/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 10/09/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

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

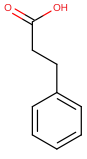
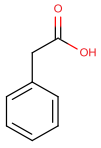
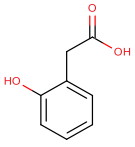
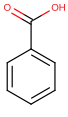
Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110601.

Appendix

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also 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, 2016).

- 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 substance 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material	Read-across Material	Weight of Evidence
Principal Name	3-Phenylpropionic acid	Phenylacetic acid	2-Hydroxyphenylacetic acid	Benzoic acid
CAS No.	501-52-0	103-82-2	614-75-5	65-85-0
Structure				
Similarity (Tanimoto score)	1	0.76623	0.53571	0.699
Read-across endpoint		• Genotoxicity • Developmental • Skin sensitization	• Genotoxicity	• Genotoxicity
Molecular Formula	$C_9H_{10}O_2$	$C_8H_8O_2$	$C_8H_8O_3$	$C_7H_6O_2$
Molecular Weight	150.18	136.15	152.15	122.12

Melting Point (°C, EPI Suite)	69.30	59.25	102.93	48.85
Boiling Point (°C, EPI Suite)	282.74	266.58	312.39	249.2
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.119	0.517	0.146	0.858
Log Kow (KOWWIN v1.68 in EPI Suite)	1.84[1]	1.41[1]	0.85[1]	1.87[1]
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	5.046E+004	1.348E+004	1.317E+005	3.400E+004
J_{max} (μg/cm^2/h, SAM)	86.09407	163.3165	404.5665	120.9484
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.95E-003	4.48E-003	4.66E-007	1.08E-007
Genotoxicity				
DNA binding (OASIS v 1.1 QSAR Toolbox 3.1)	• No alert found	• No alert found	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.1)	• Michael addition	• Michael addition	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found	• No alert found	• No alert found
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	• No alert found	• No alert found
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found	• No alert found	• No alert found
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified	• Phenol type compounds	• Not classified
Repeated dose toxicity				
Repeated Dose (HESS)	• Amineptine (hepatotoxicity) alert	• Not categorized	• Not categorized	• No alert found
Reproductive and developmental toxicity				
ER Binding by OECD QSAR Tool Box (3.1)	• Non-binder, without OH or NH_2 group	• Non-binder, without OH or NH_2 group	• Weak binder, OH group	• Non-binder, without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (good reliability)	• Toxicant (good reliability)	• Toxicant (low reliability)	• Toxicant (low reliability)
Skin Sensitization				
Protein binding by OASIS v1.1	• No alert found	• No alert found	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• 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)	• Not possible to classify according to these rules (GSH)
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)	• Sensitizer (low reliability)	• Non-sensitizer
Metabolism				
OECD QSAR Toolbox (3.1) Rat liver S9 metabolism simulator	See Supplemental Data 1 • 3 metabolites from Rat S9 simulator. • No alert found.	See Supplemental Data 2 • 2 metabolites from Rat S9 simulator. • Phenols, non-covalent DNA interactions, AN2, Michael addition.	See Supplemental Data 3 • 6 metabolites from Rat S9 simulator. • Phenols, non-covalent DNA interactions, AN2, Michael addition.	• No metabolites

Summary

There are insufficient toxicity data on 3-phenylpropionic acid (CAS # 501-52-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, phenylacetic acid (CAS # 103-82-2) and 2-hydroxyphenylacetic acid (CAS # 614-75-5) were identified as read-across analogs with sufficient data for toxicological evaluation. Benzoic acid (CAS # 65-85-0) was used as an additional weight of evidence.

12. Conclusions

- Phenylacetic acid (CAS # 103-82-2) is used as a structurally similar read-across analog for 3-phenylpropionic acid (CAS # 501-52-0) for the mutagenicity, developmental, and skin sensitization toxicity endpoints.
  - o The target and analog are structurally similar and belong to a class of carboxylic acids.
  - o They have acid group substituted benzene substructures common among both.
  - o The key difference between the target material and the read-across analog is the length of the benzyl substitution acid group, which is propenoic acid in the target and acetic acid in the read-across.
  - o The target and the read-across analog have a Tanimoto score of 0.7662, which is mainly driven by the benzyl substituted acid substructure. The differences in the structures that are responsible for the Tanimoto score < 1 are not toxicologically relevant.
  - o The physical–chemical properties of the target and the read-across analog are similar.
  - o The structural alerts for the toxicological endpoints are consistent between the target and the read-across material.
  - o The structural alerts show that the predicted metabolites of the read-across material are more reactive as compared to the target material or its predicted metabolites.
  - o The structural alerts show that the read-across material is similarly reactive for the mutagenicity, developmental, and skin sensitization toxicity endpoints as compared to the target material.

- The structural alerts show that the predicted metabolites of the read-across material are more reactive as compared to the target material or its predicted metabolites.
- The target and analog are expected to be metabolized similarly, as shown by the metabolism simulator. All of the read-across metabolites show no structural alerts for the mutagenicity, developmental, or skin sensitization toxicity endpoints.
- The structural differences between target and the read-across analog appear to be toxicologically insignificant.

- 2-Hydroxyphenylacetic acid (CAS # 614-75-5) is used as a structurally similar read-across analog for 3-phenylpropionic acid (CAS # 501-52-0) for the clastogenicity endpoint.
  - The target and analog are structurally similar and belong to a class of organic acids.
  - They have acid group substituted benzene substructures common among both.
  - The key difference between the target material and the read-across is that the read-across has a hydroxy group on the 2 position.
  - The target and the read-across analog have a Tanimoto score of 0.5357, which is mainly driven by the benzyl substituted acid substructure. The differences in the structure that are responsible for the Tanimoto score < 1 are not toxicologically relevant.
  - The physical–chemical properties of the target and the read-across analog are moderately similar.
  - Structural alerts for the toxicological endpoints are consistent between the target and the read-across material.
  - The structural alerts show that the read-across material could be classified as a phenol type in oncologic classification, and the target material is not classified.
  - The structural alerts show that the predicted metabolites of the read-across material are more reactive as compared to the target material or its predicted metabolites.
  - The structural alerts for the predicted metabolic products show that the read-across material is more reactive for the clastogenicity endpoint as compared to the target material.
  - The target and analog are expected to be metabolized similarly, as shown by the metabolism simulator. All of the read-across metabolites show no structural alerts for clastogenicity toxicity.
  - The structural differences between the target and the read-across analog appear to be toxicologically insignificant.
- Benzoic acid (CAS # 65-85-0) is used as a weight of evidence for 3-phenylpropionic acid (CAS # 501-52-0) for the genotoxicity endpoint.
  - The target and analog are structurally similar. Benzoic acid is an aromatic carboxylic acid, while 3-phenylpropionic acid is an aliphatic acid with an aromatic moiety insulated from an acid group.
  - The target and read-across analog have a Tanimoto score of 0.699, which is mainly driven by the benzyl substituted acid substructure. The differences in the structure that are responsible for the Tanimoto score < 1 are not toxicologically relevant.
  - The physical–chemical properties of the target and the read-across analog are similar.
  - The structural alerts for the genotoxic endpoint are consistent between the target and the read-across material.
  - The structural alerts show that the predicted metabolites of the read-across material are more reactive as compared to the target material or its predicted metabolites.
  - The structural alerts show that the read-across material is similarly reactive for the genotoxicity endpoint as compared to the target material.
  - The target and analog are expected to be metabolized similarly, as shown by the metabolism simulator. All of the read-across metabolites show no structural alerts for the genotoxicity endpoint.
  - The structural differences between the target and the read-across analog appear to be toxicologically insignificant.

References

Anderson, H.H., Shimkin, M.B., Leake, C.D., 1936. Acute intraperitoneal toxicity of some plant growth substances for mice. PSEBM (Proc. Soc. Exp. Biol. Med.) 34, 138–139.

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Berthelot, A., Dieryck, J., 1939. Toxicity of 3-indoleacetic acid and some related acids. C.r. Seanc. Soc. Biol. 130 (14), 1524–1526.

Boggs, D.E., Rosenberg, R., Waisman, H.A., 1963. Effects of phenylalanine, phenylacetic acid, tyrosine and valine on brain and liver serotonin in rats. PSEBM (Proc. Soc. Exp. Biol. Med.) 114 (2), 356–358.

Burton, S.A., Petersen, R.V., Dickman, S.N., Nelson, J.R., 1986. Comparison of in vitro bacterial bioluminescence and tissue culture bioassays and in vivo tests for evaluating acute toxicity of biomaterials. Journal biomed. Mater. Res. Journal of Biomedical Materials Research 20 (6), 827–838.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Davies, G.E., Driver, G.W., Hoggarth, E., Martin, A.R., Paige, M.F.C., Rose, F.L., Wilson, B.R., 1956. Studies in the chemotherapy of tuberculosis: ethyl mercaptan and related compounds. Br. J. Pharmacol. 11, 351–356.

Dawson, D.A., Schultz, T.W., Hunter, R.S., 1996. Developmental toxicity of carboxylic acids to Xenopus embryos: a quantitative structure-activity relationship and computer-automated structure evaluation. Teratog. Carcinog. Mutagen. 16 (2), 109–124.

Demir, E., Kocaoglu, S., Kaya, B., 2010. Assessment of genotoxic effects of benzyl derivatives by the comet assay. Food Chem. Toxicol. 48 (5), 1239–1242.

ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. Read-across assessment framework (RAAF). Retrieved from www.echa.europa.eu/documents/10162/13628/raaf_en.pdf .

ECHA, 2017. 3-Phenylpropionic acid registration dossier. Retrieved from. https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/19419.

Hamers, A.E.P., Piersma, A.H., Verhoef, A., Jansen, E.J.H.M., Peters, P.W.J., 1989. Embryotoxicity of phenylketonuria (PKU)-related metabolites of phenylalanine (phe) in rat whole embryo culture. Teratology 40 (3), 284.

Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989. An evaluation of food flavoring ingredients in a genetic toxicity screening battery. Toxicologist 9 (1), 257.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

Hoshino, I., 1940. Behavior of Liver in the Long Continued Administration of Aromatic Compounds. Parts 4 to 6. Zikken Syokaki-Byogaku, vol. 15. pp. 117–151.

IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

Ishidate Jr., M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Food Chem. Toxicol. 22 (8), 623–636.

Jansson, T., Curvall, M., Hedin, A., Enzell, C.R., 1988. In vitro studies of the biological effects of cigarette smoke condensate. III. Induction of SCE by some phenolic and related constituents derived from cigarette smoke - a study of structure-activity relationships. Mutat. Res. Genet. Toxicol. 206 (1), 17–24.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. In: Current Problems in Dermatology, vol. 14. pp. 152–171.

Kumar, P.G., Laloraya, M., Laloraya, M.M., 1989. The effect of some of the polyphenolic compounds on sperm motility in vitro: a structure-activity relationship. Contraception 39 (5), 531–539.

Maganova, N.B., Saitsev, A.N., 1973. Study of the embryotoxic action of some synthetic food flavorings. Vopr. Pitan. 32 (4), 50–54.
OECD, 2001. SIDS initial assessment report for 13th SIAM (bern, 7th–9th november 2001). Retrieved from: https://hpvchemicals.oecd.org/UI/handler.axd?id=dbb03e9a-6b79-4042-8c70-b76b8932d8cf.
OECD, 2012. The OECD QSAR Toolbox, v3.4. Retrieved from. http://www.qsartoolbox.org/.
OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.
Oikawa, A., Tohda, H., Kanai, M., Miwa, M., Sugimura, T., 1980. Inhibitors of poly (adenosine diphosphate ribsose) polymerase induce sister chromatid exchanges. Biochem. Biophys. Res. Commun. 97 (4), 1311–1316.
RIFM (Research Institute for Fragrance Materials, Inc), 1965. Repeated Insult Patch Test with Phenylacetic Acid in Humans. Unpublished report from International Flavors and Fragrances. RIFM report number 54726. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1972. The Contact-Sensitization Potential of Fragrance Materials by Maximization Testing in Humans. Report to RIFM. RIFM Report Number 1804. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1982. Mutagenicity Evaluation of Phenylacetic Acid in the Mouse Lymphoma Forward Mutation Assay. Private Communication to FEMA. Unpublished Report from Lorillard Tobacco Company. RIFM Report Number 36392. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1983a. Mutagenicity Evaluation of Phenylacetic Acid in the Ames Salmonella/microsome Plate Test. Private Communication to FEMA. Unpublished Report from Lorillard Tobacco Company. RIFM Report Number 36393. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1983b. 14-Day Single Dose Subacute Toxicity Study in Rats with Phenylacetic Acid. Private Communication to FEMA. Unpublished Report from Lorillard Tobacco Company. RIFM Report Number 36394. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1993. Chromosome Aberrations of Ortho-Hydroxyphenylacetic Acid in Chinese Hamster Ovary (CHO) Cells. Report to RIFM. RIFM Report Number 29162. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1994a. Unscheduled DNA Synthesis of Ortho-Hydroxyphenylacetic Acid and 7-hydroxycoumarin in Rat Primary Hepatocytes. Report to RIFM. RIFM Report Number 29164. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1994b. Salmonella/Mammalian-microsome Plate Incorporation Mutagenicity Assay. (Ames Test). Report to RIFM. RIFM Report Number 29165. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2014a. Report on the Testing of 3-phenylpropionic Acid in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 67162. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2014b. Exposure Survey 05, September 2014.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Sasaki, Y.F., Kawaguchi, S., Kamaya, A., Ohshita, M., Kabasawa, K., Iwama, K., Taniguchi, K., Tsuda, S., 2002. The comet assay with 8 mouse organs: results with 39 currently used food additives. Mutation Research. Genetic Toxicology and Environmental Mutagenesis 519 (1–2), 103–119.
Schafer Jr., E.W., Bowles Jr., W.A., 1985. Acute oral toxicity and repellency of 933 chemicals to house and deer mice. Arch. Environ. Contam. Toxicol. 14, 111–129.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Sherwin, C.P., Kennard, K.S., 1919. Toxicity of phenylactic acid. Journal of Biological Chemistry. The Journal of Biological Chemistry 40, 259–264.
US EPA, 2005. FFHPVC final revised robust summaries for phenethyl alcohol. Retrieved from. https://ofmpub.epa.gov/oppthpv/document_api.download?FILE=c13895rr.pdf.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
Zaitsev, A.N., Maganova, N.B., 1975. Embryotoxic action of some food aromatizers. Vopr. Pitan. 3, 64–68.
Zaitsev, A.N., Rakhmanina, N.L., 1974. Some data on the toxic properties of phenylethanol and cinnamic alcohols. Vopr. Pitan. 6, 48–53.