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RIFM fragrance ingredient safety assessment, phenylacetic acid, CAS Registry Number 103-82-2

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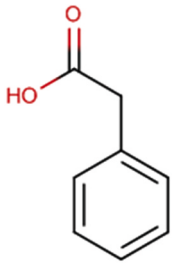
Name: Phenylacetic acid
CAS Registry Number: 103-82-2



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 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, 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,

(*continued on next column*)

(*continued*)

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.

Phenylacetic acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on phenylacetic acid and analog 2-hydroxyphenylacetic acid (CAS # 614-75-7) and WoE from benzoic acid (CAS # 65-85-0) show that phenylacetic acid is not expected to be genotoxic. Data on phenylacetic acid provide a calculated MOE >100 for the developmental toxicity endpoint. Data on analog benzoic acid (CAS # 65-85-0) provide a calculated MOE >100 for the repeated dose toxicity and fertility endpoints and show that there are no safety concerns for phenylacetic acid for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; phenylacetic acid is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; phenylacetic acid was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1983; RIFM, 1982; RIFM, 1993; Sasaki, 2002; Demir, 2010; OECD, 2001)
Repeated Dose Toxicity: NOAEL = 2.16 mg/kg/day.	(ECHA REACH Dossier: Benzoic Acid; ECHA, 2011)
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.	(RIFM, 2009; Shtenberg, 1970; ECHA, 2011; OECD, 2001; IPCS, 2018; Nair, 2001)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	RIFM (2020b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 57.8% (OECD 301D)	(ECHA REACH Dossier: Phenylacetic acid; ECHA, 2012b)
Bioaccumulation:	
Screening-level: 3.16 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 575.3 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 575.3 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.5753 μg/L

- **Revised PEC/PNECs (2015 IFRA Volume of Use):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Phenylacetic acid
2. **CAS Registry Number:** 103-82-2
3. **Synonyms:** Benzeneacetic acid; Benzylcarboxylic acid; α-Toluic acid; フェニル酢酸; Phenylacetic acid
4. **Molecular Formula:** $C_8H_8O_2$
5. **Molecular Weight:** 136.15 g/mol
6. **RIFM Number:** 307
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 266 °C (Fragrance Materials Association [FMA]), 266.58 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >212 °F; CC (FMA)
3. **Log K_{ow}:** 0.60 (MacKay, 1980) (, 1.43 (EPI Suite)
4. **Melting Point:** 76–78 (FMA), 77.0 °C (MacKay, 1980), 59.25 °C (EPI Suite)
5. **Water Solubility:** 13480 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00213 mm Hg at 20 °C (EPI Suite v4.0), 0.004 mm Hg at 20 °C (FMA), 0.00388 mm Hg at 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} • cm^{-1})
9. **Appearance/Organoleptic:** A white to off-white crystal or powder having a sweet honey top note and a floral background (Arctander, 1969).

3. Volume of use (Worldwide band)

1. 10–100 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:** 0.014% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000086 mg/kg/day or 0.0063 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00076 mg/kg/day (RIFM, 2019)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low.

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

6.2. Analogs selected

a. **Genotoxicity:** 2-Hydroxyphenylacetic acid (CAS # 614-75-7); benzoic acid (CAS # 65-85-0)
b. **Repeated Dose Toxicity:** Benzoic acid (CAS # 65-85-0)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Benzoic acid (CAS # 65-85-0)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

JECFA, 2003: Phenylacetic acid is a normal component of human urine and is known to arise mainly as a result of the breakdown of the amino acid phenylalanine by bacteria in the intestine (Seakins, 1971). Prior to excretion, phenylacetic acid is conjugated with glutamine by humans and a few other species. In most animals (rat, dog, rabbit, and horse), it is conjugated with glycine and/or glucuronic acid, but in birds, it is conjugated with ornithine (James, 1972, 1973). Conjugation with taurine occurs to a small extent among most species. For example, in 2 men orally administered ^{14}C-phenylacetic acid (1 mg/kg), 91% and 7% of the dose were excreted as the glutamine and taurine conjugates, respectively (James, 1972). Another individual fed 34 doses of phenylacetic acid (1000–10000 mg per dose) over 97 days excreted >90% of the administered dose as the phenylacetylglutamine conjugate (Ambrose, 1933). In humans, conjugation of phenylacetic acid with glutamine is facilitated by coenzyme A, as evidenced by the formation of the intermediate product, phenylacetyl-coenzyme A, which is observed prior to the formation of the phenylacetyl-glutamine conjugate (Moldave and Meister, 1957). It is known that metabolic switching can occur as large doses of phenylacetic acid can saturate preferred metabolic pathways (James, 1973). Patients with phenylketonuria form large amounts of phenylacetic acid but excrete phenylacetic acid mainly as the glutamine conjugate (James, 1973). The metabolism information available on the general metabolic pathway for phenylacetic acid suggests that humans have an adequate capacity to metabolize and eliminate phenylacetic acid when used as a fragrance ingredient.

Additional References: None.

8. Natural occurrence

Phenylacetic acid is reported to occur in the following foods by the VCF*:

Beer	Litchi (*Litchi chinensis* Sonn.)
Citrus fruits	Mustard (*Brassica* species)
Cocoa category	Peanut (*Arachis hypogaea* L.)
Honey	Rapeseed
Licorice (*Glycyrrhiza* 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. This is a partial list.

9. REACH dossier

Available; accessed on 11/05/20 (ECHA, 2012b).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, phenylacetic acid does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of phenylacetic acid 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, 1983). 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 studies assessing the clastogenicity of phenylacetic acid. The read-across material, 2-hydroxyphenylacetic acid (CAS # 614-75-5; see Section VI), 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 phenylacetic acid.

Data on read-across material benzoic acid (CAS # 65-85-05; see Section VI) was also considered as the weight of evidence (WoE) 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, 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, 1980; Jansson, 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 (Yilmaz, 2009). 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, 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 benzoic acid increased both tail moment and percent tail DNA (Demir, 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 of 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 was 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 life span 2.5–3.5 years) using male and female Swiss Albino mice given 2% sodium benzoate continuously in drinking water showed no carcinogenic effect. Taken together, benzoic acid and sodium benzoate did not exhibit genotoxic effects *in vivo* and were negative in a long-term carcinogenicity study. Hence, it can be concluded that benzoic acid does not present a concern for genetic toxicity, and this can be extended to phenylacetic acid.

Based on the available data, phenylacetic acid does not present a concern for genotoxicity.

Additional References: RIFM, 1994a; RIFM, 1994b; Heck, 1989.

Literature Search and Risk Assessment Completed On: 12/09/20.

11.1.2. Repeated dose toxicity

The MOE for phenylacetic acid is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on phenylacetic acid to support the repeated dose toxicity endpoint. Read-across material benzoic acid (CAS # 65-85-0; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In addition to the key study used to determine a conservative NOAEL (below), additional studies on benzoic acid involving other routes of administration and varying lengths are summarized in Table 1. In a GLP-compliant study equivalent or similar to an OECD 412 subacute inhalation toxicity 28-day study, Sprague Dawley CD rats (10 rats/sex/dose) were exposed to benzoic acid (purity not reported) at concentrations of 0, 25, 250, or 1200 mg/m^3 (equivalent to 0, 6.48, 64.83, or 311.19 mg/kg/day, respectively) for 6 h/day, 5 days/week, through whole-body exposure. Parameters evaluated included clinical signs (twice daily), body weight (prior to exposure and weekly thereafter), serum biochemistry, hematology, organ weights, necropsy, and histopathology. At the 1200 mg/m^3 dose, mortality in 2 rats, decreased body weight, statistically significantly decreased platelets, decreased absolute/relative liver weights, and decreased relative weight of trachea with lungs (females only) were reported. At the highest dose, absolute kidney weight and body weight were reported to be slightly decreased (though not significantly) in females compared to controls. No treatment-related gross lesions were reported in any of the tested doses for the following organs: adrenal, nasal turbinate, brain, pancreas, colon, pituitary, esophagus, prostate/uterus, the eye with the optic nerve, submaxillary salivary gland, testis (both), ovary, jejunum, Harderian glands, spleen, heart, sternum (bone marrow), kidney, stomach, liver, thymus, lungs (5 lobes), thyroid/parathyroid, bronchial lymph node, urinary bladder, and mammary gland. Treatment-related but not dose-dependent microscopic lesions were reported, which included increased inflammatory cell infiltrate and increased incidence, intensity, and extent of interstitial fibrosis in the lungs of animals from the low-, mid-, and high-dose groups. The interstitial fibrosis in the lungs was due to a local corrosive property of benzoic acid through the inhalation route. In both mid- and high-dose groups, reddish discharge around the nares was reported. At the 250 mg/m^3 dose, upper respiratory tract irritation was

Table 1
Additional animal studies that were conducted on benzoic acid.

Duration in Detail	GLP/Guideline	No. of Animals/ Dose (Species, Strain, Sex)	Route (Vehicle)	Doses (in mg/kg/day; Purity)	NOAEL/LOAEL/ NOEL	Justification of NOAEL/ LOAEL/NOEL	References
90-day	Not reported; non-GLP and non-guideline study	50 mice/dose/sex (cross-bred white)	Oral (gavage)	80 mg/kg/day. (Note: 14 surviving mice were subjected to a restricted dietary intake [90% restriction] for up to 5 days)	LOAEL: 80 mg/kg/ day	✓ Highest mortality rate 85.7% (56.3% in controls) after 5 days on restricted diet	Shtenberg (1970)
504-day	Not reported; non-GLP and non-guideline study	Wistar Rats; 20 males and 30 females; control group 13 males and 12 females	Oral (diet)	1.5% in diet (approximately 1125 mg/kg/day)	LOAEL: 1125 mg/ kg/day	✓ Reduced feed intake, growth retardation, increased mortality rate (15/50 vs. 3/25 in the control)	OECD, 2001
250 days	Not reported; non-GLP and non-guideline study	Dogs (strain and sex not reported) 17/dose	Oral (Diet)	1000 mg/kg/day	LOAEL: 1000 mg/ kg/day	✓ At higher doses ataxia, epileptic convulsions, and mortality reported	IPCS (2018)
52 weeks	Not reported; non-GLP and non-guideline study	Sprague Dawley rats, 20/sex/dose	Oral (Diet)	0.5% or 2% (approximately 250 or 1000 mg/kg/day)	NOAEL: 1000 mg/ kg/day	✓ No effects up to highest tested dose	Nair (2001)
4-week 6 h/day; 5 days/ week	GLP/OECD 412	10/dose/Crl:CD (SD) rats/sex	Inhalation (nose-only)	0 (Control group, filtered air) 2.5 and 12.5 mg/m^3 (0.65 and 3.24 mg/kg/day)	NOAEL: 12.6 mg/ m^3 (3.24 mg/kg/ day)	✓ No effects up to highest tested dose	RIFM (2009)
21 days	GLP (EPA OPP 82-2), 21-day (5 days/week) repeated dose dermal toxicity study	New Zealand White rabbits (4 rabbits/sex/dose)	Dermal	100, 500, 2500 mg/kg/day	NOAEL: 2500 mg/ kg/day	✓ No systemic adverse effects observed up to highest tested dose	ECHA (2011)
35 days	Not reported; non-GLP and non-guideline study	Male Wistar rats (5–10 rats/dose)	Oral (diet)	0%, 1.1%, and 3.0% (approximately 0, 825, and 2250 mg/kg/day, respectively)	NOAEL: 1.1% (approximately 825 mg/kg/day)	✓ At higher doses, adverse effects reported for mortality, bodyweight gain, metabolic changes, and histopathology	ECHA (2011)
8 weeks	Not reported; non-GLP and non-guideline study	Strain not reported); 40 rats/ group (20/sex/ group)	Oral (diet)	0%, 0.5%, 1%, and 5% (equivalent to 0, 250, 500, and 2500 mg/kg/day, respectively)	NOAEL: 1% (approximately 500 mg/kg/day)	✓ Diet intolerance of rats to benzoate and mortality of all the rats at the highest dose tested	OECD (2001)

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

observed, which was confirmed by inflammatory exudate around the nares. Based on the presence of systemic effects observed at 1200 (the highest tested dose) and 250 mg/m^3, the no observed adverse effect concentration (NOAEC) was considered to be 25 mg/m^3, although local effects were observed at the low dose predominantly due to the local corrosive property of benzoic acid (ECHA, 2011).

As WoE, data from other studies on benzoic acid are shown in the table below (see Table 1).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day repeated dose study (ECHA, 2012a). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 6.48/3 or 2.16 mg/kg/day.

Therefore, the phenylacetic acid MOE for the repeated dose toxicity endpoint can be calculated by dividing the benzoic acid NOAEL by the total systemic exposure for phenylacetic acid, 2.16/0.00076, or 2842.

In addition, the total systemic exposure to phenylacetic acid (0.76 μg/kg/day) is below the TTC (30 μg/kg/day); (Kroes, 2007) for the repeated dose endpoint for Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/10/20.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on phenylacetic acid or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to phenylacetic acid (0.76 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/14/22.

11.1.4. Skin sensitization

Based on the existing data and the read-across material, benzoic acid (CAS # 65-85-0), phenylacetic acid does not present a concern for skin sensitization under the current declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for phenylacetic acid. The chemical structure of phenylacetic acid and the read-across benzoic acid indicates that they would not be expected to react significantly with skin proteins directly (Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, benzoic acid, was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA) (Natsch, 2013a) and negative in KeratinoSens and U937-CD86 tests (Natsch, 2013a, 2013b). In a murine local lymph node assay (LLNA), benzoic acid was not found to be sensitizing up to 20% (Gerberick, 1992; ECHA, 2011). In guinea pig open epicutaneous tests (OET), phenylacetic acid did not exhibit the potential to induce skin sensitization (Klecak, 1985). In a guinea pig maximization test with the read-across material, benzoic acid did not present reactions indicative of sensitization up to 20% (Gad, 1986; ECHA, 2011). In guinea pig Freund's Complete

Adjuvant Test (FCAT), reactions were reported with the read-across material benzoic acid at 10% (Hausen, 1992, 1995). However, limited details on the study protocol and the reactions were provided. In a human maximization test, no reactions indicative of sensitization were observed at the maximum tested concentration of 2% (1380 μg/cm^2) in 25 volunteers (RIFM, 1972). In a human repeat insult patch test (HRIPT), 0.125% phenylacetic acid in alcohol SDA39C did not produce reactions indicative of sensitization in any of the subjects tested (RIFM, 1965). In 2 human maximization tests with the read-across material, no skin sensitization reactions were observed with benzoic acid at 2% (1380 μg/cm^2) and 5% (3450 μg/cm^2) (RIFM, 1977; Leyden, 1977). Additionally, in a confirmatory HRIPT with 992 μg/cm^2 of benzoic acid in 3:1 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 113 volunteers (RIFM, 2020b). Based on the WoE from animal and human studies and the data on the read-across material, phenylacetic acid does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: Gad (1986); McKim (2012); Piroird (2015); Emter (2010); McKim (2010); Alepee (2015); ECHA, 2011.

Literature Search and Risk Assessment Completed On: 12/16/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, phenylacetic acid 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 phenylacetic acid in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, phenylacetic acid 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 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} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/04/20.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are limited inhalation data available on phenylacetic acid. Based on the Creme RIFM Model, the inhalation exposure is 0.0063 mg/day. This exposure is 222 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Engstrom (1984).

Literature Search and Risk Assessment Completed On: 11/19/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of phenylacetic acid was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{ow}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high UF 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 UF 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 UFs. 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, phenylacetic 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 is < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify phenylacetic acid as 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, 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 $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

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

11.2.2. Key studies

11.2.2.1. Biodegradation. No data available.

11.2.2.2. Ecotoxicity. No data available.

11.2.2.3. Other available data. Phenylacetic acid has been registered under REACH with the following additional data available at this time (ECHA, 2012b):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 57.8% was observed after 35 days.

A biodegradation study was conducted according to the OECD screening test. The percentage degradation of the test chemical was determined to be 100% by DOC, GC, and HPLC parameters after a period of 3 days.

The acute fish (*Danio rerio*) toxicity test was conducted according to the OECD 203 guidelines under static conditions. The 96-h LC0 value, based on nominal test concentration, was reported to be 100 mg/L.

A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value, based on nominal test concentration, was reported to be 52.5 mg/L (95% CI: 46.2–59.7 mg/L).

A 7-day algae growth inhibition test was conducted under static

conditions. The 7-day EC50 value, based on measured test concentration for growth inhibition, was reported to be 177 mg/L.

11.2.2.4. Risk assessment refinement. Since phenylacetic 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.43	1.43
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<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 0.5753 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the 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: 12/01/20.

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 03/15/22.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113240.

Appendix

Read-across Justification

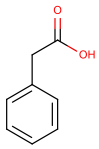
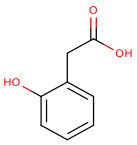
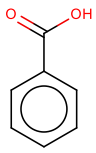
Methods

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC) (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	575.3			1000000	0.5753	

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	Phenylacetic acid	2-Hydroxyphenylacetic acid	Benzoic acid
CAS No.	103-82-2	614-75-5	65-85-0
Structure			
Similarity (Tanimoto score)		0.71	0.41
Read-across endpoint		• Genotoxicity	• Repeated dose toxicity • Fertility • Skin sensitization • Genotoxicity
Molecular Formula	$C_8H_8O_2$	$C_8H_8O_3$	$C_7H_6O_2$
Molecular Weight (g/mol)	136.15	152.15	122.12
Melting Point (°C, EPI Suite)	59.25	102.93	48.85
Boiling Point (°C, EPI Suite)	266.58	312.39	249.2
Vapor Pressure (Pa at 25 °C, EPI Suite)	0.517	0.146	0.858
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	1.41[1]	0.85[1]	1.87[1]
Water Solubility (mg/L, at 25 °C, WSKOW v1.42 in EPI Suite)	1.348E+004	1.317E+005	3.400E+004
J_{max} (mg/cm^2/h, SAM)	163.3165	404.5665	120.9484
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	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
DNA binding by OECD QSAR Toolbox (v3.1)	• Michael addition	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• 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
***In vitro* mutagenicity (Ames test) alerts by ISS**	• No alert found	• No alert found	• No alert found
***In vivo* mutagenicity (Micronucleus) alerts by ISS**	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor	• No alert found
Oncologic Classification	• Not classified	• Phenol-type compounds	• Not classified
Repeated dose toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	• No alert found
Reproductive and developmental toxicity			
ER Binding by OECD QSAR Toolbox (v3.1)	• 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 (low reliability)	• Toxicant (low reliability)
Sensitization			
Protein binding by OASIS v1.1	• No alert found	• No alert found	• No alert found
Protein binding by 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)

(*continued on next page*)

(*continued*)

	Target material	Read-across Material	Read-across Material
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• AN2 Michael addition	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (low reliability)	• NON-sensitizer
Metabolism			
OECD QSAR Toolbox (v3.1) Rat liver S9 metabolism simulator	Supplemental Data 1	Supplemental Data 2	No metabolites

Summary

There is insufficient toxicity data on phenylacetic acid (CAS # 103-82-2). 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, read-across analogs 2-hydroxyphenylacetic acid (CAS # 614-75-5) and benzoic acid (CAS # 65-85-0) were identified as read-across materials with sufficient toxicological data.

Conclusions

- 2-Hydroxyphenylacetic acid (CAS # 614-75-5) was used as a structurally similar read-across analog for phenylacetic acid (CAS # 103-82-2) for the genotoxicity (clastogenicity) endpoint.
  - o The target material and read-across analog are structurally similar and belong to a class of carboxylic acids.
  - o They have a phenylacetic acid substructure common among both.
  - o The key difference between the target material and the read-across is that the read-across has a hydroxyl group at the 2 position.
  - o The target material and read-across analog have a Tanimoto score of 0.5974, which is mainly driven by the benzene ring substructure. The differences in the structure that are responsible for a Tanimoto score <1 are not relevant from a toxicology endpoint perspective.
  - 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 read-across material is more reactive for the clastogenicity endpoint as compared to the target material.
  - o 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.
  - o The structural alerts show that the predicted metabolites of the read-across material are similarly reactive as compared to the target material or its predicted metabolites.
  - o The target material and read-across 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.
  - o The structural differences between the target and the read-across analog appear to be toxicologically insignificant.
- Benzoic acid (CAS # 65-85-0) was used as a structurally similar read-across analog for phenylacetic acid (CAS # 103-82-2) for the genotoxicity, skin sensitization, repeated dose toxicity, and fertility endpoints.
  - o The target material and read-across analog are structurally similar and belong to a class of carboxylic acids.
  - o Both have a benzene substructure.
  - o The key difference between the target material and the read-across analog is that the read-across has a carboxyl substituent, whereas the target has a carboxymethyl substituent on the benzene ring.
  - o The target material and read-across analog have a Tanimoto score of 0.6666, which is mainly driven by the benzene ring substructure. The differences in the structure that are responsible for a Tanimoto score <1 are not relevant from a toxicology endpoint perspective.
  - o The physical-chemical properties of the target material 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 read-across material is similarly reactive for the repeated dose and reproductive toxicity endpoints as compared to the target material.
  - o The structural alerts show that the predicted metabolites of the read-across material are similarly reactive as compared to the target material or its predicted metabolites.
  - o OECD QSAR Toolbox v4.2 showed that the read-across had observed metabolites with no structural alerts for repeated dose and reproductive toxicological endpoints. The target material did not have any observed metabolites.
  - o The structural differences between the target material and the read-across analog appear to be toxicologically insignificant.

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