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RIFM fragrance ingredient safety assessment, benzoic acid, CAS Registry Number 65-85-0

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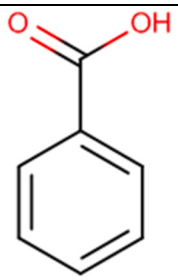

Name: Benzoic acid
CAS Registry Number: 65-85-0

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
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; Safford et al., 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
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

(*continued on next column*)

(*continued*)

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.

Benzoic acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that benzoic acid is not genotoxic. Data on benzoic acid provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints. Data show that there are no safety concerns for benzoic acid for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; benzoic acid is not phototoxic/not expected to be photoallergenic. The environmental endpoints were evaluated; benzoic acid was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(Zeiger et al., 1988; ECHA REACH Dossier: Benzoic acid; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 2.16 mg/kg/day.	(ECHA REACH Dossier: Benzoic Acid; ECHA, 2011)
Reproductive Toxicity: Developmental toxicity and fertility NOAEL = 1069 mg/kg/day.	(Turnbull et al., 2021; Kieckebusch and Lang, 1960)
Skin Sensitization: Not a sensitization concern under the current, declared levels of use.	(RIFM, 2020; ECHA REACH Dossier: Benzoic acid, ECHA, 2011; Natsch et al., 2013a; Natsch and Haupt, 2013b)
Phototoxicity/Photoallergenicity: Not phototoxic, not expected to be photoallergenic.	(UV/Vis Spectra, RIFM Database; Duffy et al., 1987; Duffy et al., 1989)
Local Respiratory Toxicity: NOAEC = 2.5 mg/m^3	(ECHA REACH Dossier: Benzoic Acid; ECHA, 2011)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.0 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 3.1 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 213.7 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: 213.7 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.2137 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Benzoic acid
2. **CAS Registry Number:** 65-85-0
3. **Synonyms:** Benzenecarboxylic acid; Dracylic acid; Unisept BZA; Dracyclic acid; Benzenemethanoic acid; Phenylformic acid; Phenylcarboxylic acid; Benzeneformic acid; Carboxybenzene; 安息香酸; Benzoic acid
4. **Molecular Formula:** $C_7H_6O_2$
5. **Molecular Weight:** 122.12 g/mol
6. **RIFM Number:** 874
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 249 °C (Fragrance Materials Association [FMA] Database), 249.51 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA Database), >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** Log Pow = 0.86 (Mackay et al., 1980), 1.87 (EPI Suite)
4. **Melting Point:** 120 °C (FMA Database), 122.4 °C (Mackay et al., 1980), 48.85 °C (EPI Suite)
5. **Water Solubility:** 2493 mg/L (EPI Suite)
6. **Specific Gravity:** Not available
7. **Vapor Pressure:** 0.00298 mm Hg at 25 °C (EPI Suite), 0.00163 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** White crystals, scales, or needles; odorless or with a slightly benzoin-like or benzaldehyde-like odor

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 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:** 0.073% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.000040 mg/kg/day or 0.0029 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0015 mg/kg/day (RIFM, 2018)

*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).

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:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

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

Acerola (*Malpighia*)	Malt
Apple fresh (*Malus* species)	*Mangifera* species
Apricot (*Prunus armeniaca* L.)	Mentha oils
Arctic bramble (*Rubus arcticus* L.)	Milk and milk products
Avocado (*Persea americana* Mill.)	Mushroom
Banana (*Musa sapientum* L.)	Noni (*Morinda citrifolia* L.)
Beef	Nutmeg (*Myristica fragrans* Houttuyn)
Beer	Omija fruit (*Schisandra chinensis* Baillon)
Black chokeberry juice (*Aronia melanocarpa* Ell.)	Papaya (*Carica papaya* L.)
Blue cheeses	Passion fruit (*Passiflora* species)
Buckwheat	Peach (*Prunus persica* L.)
Cape gooseberry (*Physalis peruviana* L.)	Pepper (*Piper nigrum* L.)
Capers (*Capparis spinoza*)	Pineapple (*Ananas comosus*)
Cheddar cheese	Plum (*Prunus* species)
Cheese, various types	Pork
Cherimoya (*Annona cherimolia* Mill.)	Potato (*Solanum tuberosum* L.)
Cherry (*Prunus avium* [sweet], pr. *Cerasus* [sour])	Rambutan (*Nephelium lappaceum* L.)
Chinese quince (*Pseudocydonia sinensis* Schneid)	Raspberry, blackberry, and boysenberry
Cider (apple wine)	Rice (*Oryza Sativa* L.)
Cinnamomum species	Rum
Citrus fruits	Rye bread
Cloudberry (*Rubus chamaemorus* L.)	Sake
Cloves (*Eugenia caryophyllata* Thunberg)	Sherry
Cocoa category	Shoyu (fermented soya hydrolysate)
Fish	Soybean (*Glycine max*. L. Merr.)
Grape (*Vitis* species)	Starfruit (*Averrhoa carambola* L.)
Grape brandy	Strawberry (*Fragaria* species)
Guava and feyoa	Sugar molasses
Honey	Swiss cheeses
Hop (*Humulus lupulus*)	Tamarind (*Tamarindus indica* L.)
Katsuobushi (dried bonito)	Tapereba, caja fruit (*Spondias lutea* L.)
Kiwifruit (*Actinidia chinensis*, syn. *A. deliciosa*)	Tea
Kumazasa (*Sasa albo-marginata*)	Thyme (*Thymus* species)
Lamb and mutton	Tomato (*Lycopersicon esculentum* Mill.)
Licorice (*Glycyrrhiza* species)	*Vaccinium* species
Loganberry juice (*Rubus ursinus* var. *Loganobaccus*)	Vanilla
Loquat (*Eriobotrya japonica* Lindl.)	Wheaten bread
Maize (*Zea mays* L.)	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.

9. REACH Dossier

Available; accessed 02/17/21 (ECHA, 2011).

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, benzoic acid does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of benzoic acid has been evaluated in a bacterial reverse mutation assay conducted in an equivalent manner to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA97 were treated with benzoic acid in dimethyl sulfoxide (DMSO) at concentrations up to 10,000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Zeiger et al., 1988). Under the conditions of the study, benzoic acid was not mutagenic in the Ames test.

The clastogenicity of benzoic acid was assessed in an *in vitro* chromosome aberration study. Chinese hamster lung cells were treated with benzoic acid in DMSO at a concentration of 1.5 mg/mL (1500 μg/mL) in the absence of metabolic activation. Ambiguous statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed at this concentration of the test material without S9 metabolic activation (ECHA, 2011). Under the conditions of the study, benzoic acid was considered to be ambiguous in the *in vitro* chromosome aberration assay.

Due to the results and the limited concentrations tested of the chromosome aberration study, the clastogenic activity of benzoic acid was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Mouse lymphoma L5178Y were treated with benzoic acid in DMSO, and micronuclei analysis was conducted at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation. Benzoic acid did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (ECHA, 2011). Under the conditions of the study, benzoic acid was considered to be non-clastogenic in the *in vitro* micronucleus test.

The results of the *in* vitro chromosome aberration study for benzoic acid can be considered not biologically relevant due to only being performed with 1 concentration and due to the use of Chinese hamster lung

Table 1
Additional animal studies 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 a restricted diet	Shtenberg and Ignat'ev, 1970; HSDB, 2021
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)
7-, 14-, or 35-day	Not reported; non-GLP and non-guideline study	No of animals not reported/Rat/ Wistar	Oral	1.1% (approximately 550 mg/kg/day)	LOAEL: 550 mg/ kg/day	✓ Significantly poor weight gain	HSDB (2021)
28-day	Not reported; non-GLP and non-guideline study	Rats (strain not reported) 10 males/dose	Oral (Diet)	0, 760, 3800 or 7600 ppm via diet (approx. 0, 65, 324, or 647 mg/kg/day)	NOAEL: 647 mg/ kg/day	✓ No adverse effects reported up to the highest dose tested	ECHA (2011)
Not reported	Not reported	Rat (no. of animals, strain, sex not reported)	Exposure	up to approximately 500 mg/kg/day	Not reported	✓ No neurotoxicity observed	NICNAS (2020)
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 teste 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 teste 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 the 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 of the rats at the highest dose tested	OECD (2001)

cells. Chinese hamster lung cells are a p53-deficient cell line that has been shown to result in a higher frequency of "misleading" positive results (Fowler et al., 2012). As an additional weight of evidence (WoE), sodium benzoate (CAS # 532-32-1) was found to be negative in an *in vivo* mammalian bone marrow chromosome aberration test, which followed guidelines in an equivalent manner to OECD 475 (ECHA, 2011).

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/12/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on benzoic acid. 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 as weight of evidence (WoE). 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 over 4 weeks. Parameters that were evaluated included clinical signs (twice daily), body weight (prior to exposure and thereafter weekly), serum biochemistry, hematology, organ weights, and histopathology. At the highest (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 inhalational route. In both mid- and high-dose groups, reddish discharge around the nares was reported. At the mid (250 mg/m^3) dose, upper respiratory tract irritation was 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 low dose predominantly due to the local corrosive property of benzoic acid (ECHA, 2011).

In a GLP and OECD 412-compliant study, 10 Crl:CD(SD) rats/sex/dose were administered benzoic acid via inhalation (nose-only) at doses of 0, 2.5, and 12.5 mg/m^3 (equivalent to 0, 0.65, and 3.24 mg/kg/day) for 4 weeks (5 days/week; 6 h/day). Based on no effects seen up to the highest dose, the NOAEL was considered to be 3.24 mg/kg/day (RIFM, 2009; see Table 1).

The NOAEL was determined from the OECD 412 study on Sprague Dawley rats (ECHA, 2011). A default safety factor of 3 was used when deriving a NOAEL from the 28-day repeated dose study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

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

Therefore, the benzoic acid MOE for the repeated dose toxicity endpoint can be calculated by dividing the benzoic acid NOAEL by the total systemic exposure for benzoic acid, 2.16/0.0015, or 1440.

In addition, the total systemic exposure to benzoic acid (1.5 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose endpoint for Cramer Class I material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/19/21

11.1.3. Reproductive toxicity

The MOE for benzoic acid is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on benzoic acid. In an OECD 443/GLP Extended One-Generation Reproductive Toxicity (EOGRT) study, conducted in Sprague Dawley rats, groups of 25 rats/sex/dose were administered benzoic acid in the diet at concentrations 0, 7500, 11,500, or 15,000 ppm (Equivalent to 526, 821, and 1069 mg/kg/day for P0 males and females, 499, 747, and 987 mg/kg/day for F1 males and 535, 790, and 1024 mg/kg/day for F1 females). Males were administered benzoic acid in the diet for 2 weeks prior to mating and continuing until euthanasia (10–11 weeks) for 6 weeks (2 weeks prior to mating) and females were treated for 6 weeks (2 weeks before mating, throughout gestation, and for 4 days after parturition). For females, benzoic acid was continuously administered in the diet for 2 weeks prior to mating and continuing throughout mating (2 weeks), gestation (3 weeks), and lactation (3 weeks), until euthanasia (10–11 weeks). In addition, the offspring selected for the F1 and F2 generations were administered benzoic acid in the diet beginning at weaning and continuing until euthanasia. In the parental generation, no treatment-related effects were seen on survival, clinical observations, organ weights, and necropsy/histopathology. Reproductive parameters were also unaffected by benzoic acid administration. In the F1 generation, no treatment-related effects were seen on survival, growth and developmental landmarks, organ weights, or necropsy/histopathology. In addition, clinical pathology (hematology, serum chemistry, urinalysis, bile acids, and thyroid hormones) and reproductive performance were also unaffected. Similarly, no adverse effects were observed in the F2 generation. Therefore, the NOAEL for developmental toxicity and fertility in the current study was 15,000 ppm (equivalent to 1069 mg/kg/day in males and females), the highest dose tested (Turnbull et al., 2021).

There are sufficient reproductive toxicity data on benzoic acid. In a non-GLP, 4-generation oral reproductive toxicity study, groups of 20 rats/sex/dose/generation were fed diets containing benzoic acid at doses of 0%, 0.5%, and 1% (equivalent to 0, 450, and 900 mg/kg/day for males and 0, 600, and 1176 mg/kg/day for females, as per the ECHA Dossier). The first generation was exposed for 8 weeks and then allowed to mate (1:1 for a period of 14 days). Mating was repeated in week 48 to raise a second litter. The first and second generations were treated for a lifetime; the third generation was treated for 16 weeks, and the fourth generation was treated up to breeding. No treatment-related adverse effects on fertility or the development of pups were reported in all 4 generations. The NOAEL for fertility effects and maternal and developmental toxicity was considered to be 1%, the highest dose tested (Kieckebusch and Lang, 1960; also available on ECHA, 2011). The most conservative NOAEL of 900 mg/kg/day was selected for the reproductive toxicity endpoint for this study.

Overall, a NOAEL from a more robust OECD 443 was considered

for the safety assessment. Therefore, the benzoic acid MOE for the developmental toxicity and fertility endpoint can be calculated by dividing the benzoic acid NOAEL in mg/kg/day by the total systemic exposure to benzoic acid, 1069/0.0015, or 712,667. Benzoic acid did not cause any adverse effects in the fertility or the development of pups in the 4-generation study. In addition, sodium benzoate has also been extensively reviewed by SCCP (2005), OECD (2001), WHO (2005), and EFSA, in which studies on different species have been conducted; see below for a summary. Results from these studies indicate that embryotoxic and fetotoxic effects, as well as malformations, were observed only at doses that induced severe maternal toxicity. In a dietary study in rats, a NOAEL of 1310 mg/kg/day was established for sodium benzoate. Thus, sodium benzoate is unlikely to have adverse developmental effects at dose levels not toxic to the mother.

Data from additional studies are provided in Table 2 as WoE

Additional References: ECHA, 2011; OECD 2001; WHO, 2005; EFSA, 2016; SCCP, 2005.

Literature Search and Risk Assessment Completed On: 02/19/21

11.1.4. Skin sensitization

Based on the existing data, benzoic acid does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, benzoic acid is not considered to be a skin sensitizer under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Benzoic acid was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA) (Natsch and Haupt, 2013b) and negative in KeratinoSens and U937-CD86 tests (Natsch et al., 2013a; Natsch and Haupt, 2013b). In a murine local lymph node assay (LLNA), benzoic acid was not found to be sensitizing up to 20% (Gerberick et al., 1992; ECHA, 2011). In a guinea pig maximization test, benzoic acid did not present reactions indicative of sensitization up to 20% (Gad et al., 1986; ECHA, 2011). In guinea pig Freund's Complete Adjuvant Test (FCAT), reactions were reported with benzoic acid at 10% (Hausen et al., 1995; Hausen et al., 1992). However, limited details on the study protocol and the reactions were provided. In a human maximization test, no skin sensitization reactions were observed with benzoic acid at 2% (1380 μg/cm^2) and 5% (3450 μg/cm^2) (RIFM, 1977; Leyden and Kligman, 1977). Additionally, in a Confirmation of No Induction in Humans test (CNIH) 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, 2020).

Based on WoE from structural analysis and animal and human studies, benzoic acid does not present a concern for skin sensitization under the current, declared levels of use.

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

Literature Search and Risk Assessment Completed On: 01/16/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra and study data, benzoic acid would not be expected to present a concern for phototoxicity. Based on the available UV/Vis spectra, benzoic acid would not be expected to present a concern for photoallergenicity.

11.1.5.1. Risk assessment. 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). In *in vitro* phototoxicity assays with 3T3 Swiss mouse fibroblasts, there was no evidence of phototoxicity (Duffy et al., 1987; Duffy et al., 1989). Based on the lack of absorbance and *in vitro* study data, benzoic acid does not present a concern for phototoxicity. Based on the lack of absorbance, benzoic acid does not present a concern for 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 et al., 2009).

Additional References: Larmi (1989).

Literature Search and Risk Assessment Completed On: 01/11/21.

11.1.6. Local Respiratory Toxicity

The MOE for benzoic acid is adequate for the respiratory endpoint at the current level of use.

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 28-day OECD 412, GLP-compliant study, Sprague Dawley CD rats (10/sex/dose) were exposed to benzoic acid at concentrations of 0, 25, 250, or 1200 mg/m^3 for 6 h/day, 5 days/week, through whole-body inhalation exposure for 4 weeks (ECHA, 2011). Standard endpoints evaluated included clinical signs, body weight, serum biochemistry, hematology, organ weight, necropsy (heart, kidney, lungs/trachea, brain, liver, and spleen), and histopathological examination. Treatment-related but not dose-dependent microscopic lesions were reported in the lungs of animals from the low-, mid-, and high-dose groups, which included increased inflammatory cell infiltrate and increased incidence, intensity, and extent of interstitial fibrosis. 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 observed, which was confirmed by inflammatory exudate around the nares. Additionally, at the 250 mg/m^3 dose, decreased relative weight of trachea with lungs (females) were reported. The effects observed in the mid-dose of 250 mg/m^3 were confined to local effects observed in the respiratory tract. Based on the observations in the lungs, the local effects LOAEC was identified at 25 mg/m^3. Using a safety factor of 10, the estimated NOAEC is 2.5 mg/m^3.

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

- (2.5 mg/m^3) × (1 m^3/1000 L) = 0.0025 mg/L
- MV of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.0025 mg/L) × (61.2 L/d) = 0.153 mg/day
- (0.153 mg/day)/(0.0016 kg lung weight of rat*) = 95.63 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0029 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015 and Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.0045 mg/kg lung weight/day resulting in a MOE of 21,251 (i.e., [95.63 mg/kg lung weight of rat/day]/[0.0045 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.0029 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

Table 2
Additional studies for reproductive toxicity.

Duration in Detail	GLP/ Guideline	No. of Animals/ dose (Species, Strain, Sex)	Test Chemical/Route (Vehicle)	Doses (in mg/kg/day; Purity)	NOAEL/LOAEL/ NOEL	Justification of NOAEL/ LOAEL/NOEL	Reference
Day 9	Non-guideline	Wistar: pregnant female rats (7/ group)	Benzoic acid/oral gavage (0.2% carboxymethylcellulose)	0 or 510 mg/kg/day	Developmental toxicity NOAEL = 510 mg/kg/day	Resorption rates and malformations comparable to control animals	Kimmel et al., 1971
GD 0 through lactation and up to 45 days of age	Non-guideline study	Wistar: pregnant female rats (10/ group)	Sodium benzoate (read-across)/oral (diet)	0%, 0.1%, 0.5%, or 1% (equivalent to 0, 50, 250, and 500 mg/kg/day, respectively)	Developmental toxicity NOAEL = 500 mg/kg/day	No treatment-related adverse effects reported	EFSA (2016)
GD 6 to 15	Similar to OECD 414/ non-GLP	Wistar: pregnant female rats (24/ group)	Sodium benzoate (read-across)/oral gavage (water)	0, 1.75, 8, 38, or 175 mg/kg/day, positive control group received aspirin	Developmental toxicity NOAEL = 175 mg/kg/day	No treatment-related adverse effects were reported	ECHA (2011)
GD 6 to 15	Similar to OECD 414/ non-GLP	CD-1: pregnant female mice (25–31/group)	Sodium benzoate (read-across)/oral gavage (water)	0, 1.75, 8.0, 38, or 175 mg/kg/day, positive control group received aspirin	Developmental toxicity NOAEL = 175 mg/kg/day	No treatment-related adverse effects were reported	ECHA (2011)
GD 6 to 18	Non-guideline	Dutch belted: pregnant (artificially inseminated) female rabbits (10–12/group)	Sodium benzoate (read-across)/oral gavage	0, 2.5, 12, 54, or 250 mg/kg/day	Developmental toxicity NOAEL = 250 mg/kg/day	No treatment-related adverse effects were reported	OECD (2001)
GD 6 to 10	Non-guideline	Golden: pregnant female hamsters (22/group)	Sodium benzoate (read-across)/Oral gavage	0, 3, 14, 65, or 300 mg/ kg/day	Developmental toxicity NOAEL = 300 mg/kg/day	No treatment-related adverse effects were reported	OECD (2001)
GD 0 to 20	Non-guideline	Wistar: pregnant female rats (27–30/group)	Sodium benzoate (read-across)/Oral (diet)	0, 1%, 2%, 4%, or 8% (equivalent to 0, 700, 1310, 1875, and 965 mg/kg/day, respectively, calculated as per actual dose taken by animals with correlation to feed intake)	Developmental toxicity NOAEL = 2% or 1310 mg/ kg/day	Treatment-related changes reported at concentrations ≥4%. •Mortality at concentrations ≥4% (convulsions and depressed motor activity) •Decreased feed consumption and body weight (statistical significance not reported). •Statistically significant increase in the number of dead or resorbed fetuses and a statistically significant decrease in bodyweight gain of fetuses •Statistically significant pathological changes were reported: eye, brain, and kidneys, in addition, abnormalities of the skeletal system (cerebral hypoplasia, delayed ossification in lumbar or cervical ribs, and varied sternebrae) •Decreased delivery rates by 50% and 8.2% at the 4% and 8% dose levels, respectively, with complete loss of litters after parturition among dams that delivered naturally •These findings in the 4% and 8% dose groups were due to malnutrition caused by a marked decrease in feed consumption because the actual feed intake at 8% was found to be less than 2%	OECD (2001)

In addition, the total systemic exposure to benzoic acid (1.5 μg/kg/day) is below TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: RIFM, 2009; HSDB, 2021.

Literature Search and Risk Assessment Completed On: 02/07/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of benzoic 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, benzoic 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 v4.11 (US EPA, 2012a) did not identify benzoic acid as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\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).

11.2.2. Risk assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Benzoic acid has been registered under REACH, and the following data is available (ECHA, 2011):

A fish (Rainbow trout) acute toxicity study was conducted according to the EPA-660/3-75-001 guideline under static conditions. The 96-h LC50 value based on nominal test concentration was reported to be 47.3 mg/L (95% CI: 40.6–55.2 mg/L).

A fish (Bluegill sunfishes) acute toxicity study was conducted according to the EPA-660/3-75-001 guideline under static conditions. The 96-h LC50 value based on nominal test concentration was reported to be 44.6 mg/L (95% CI: 39.8–50.1 mg/L).

A 28-day fish (*Oncorhynchus mykiss*) juvenile growth test was conducted according to the OECD 215 guideline under semi-static conditions. The 28-day EC50 value and NOEC value based on nominal test concentration were reported to be greater than 120 mg/L.

A *Daphnia magna* acute toxicity study was conducted according to the EPA-660/3-75-009 guideline under static conditions. The 48-h EC50 value based on nominal test concentration was reported to be greater than 100 mg/L.

A *Daphnia magna* reproduction test was conducted according to the OECD 211 guideline under semi-static conditions. The 21-day EC50 value and NOEC value based on nominal test concentration were reported to be greater than 25 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 values based on time-weighted average concentration for growth rate and yield were reported to be greater than 33.1 mg/L and 11 mg/L, respectively.

11.2.3. Risk assessment refinement

Since benzoic acid has passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>213.7</u>			1000000	0.2137	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	1.87	1.87
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.2137 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 01/05/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/21/22.

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.

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