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Short Review

RIFM fragrance ingredient safety assessment, phenylethyl anthranilate, CAS Registry Number 133-18-6

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ABSTRACT

The existing information supports the use of this material as described in this safety assessment. Phenylethyl anthranilate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from phenylethyl anthranilate and the read-across analog cinnamyl anthranilate (CAS # 87-29-6) show that phenylethyl anthranilate is not expected to be genotoxic. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class II material, and the exposure to phenylethyl anthranilate is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). Data on read-across analogs phenethyl alcohol (CAS # 60-12-8) and anthranilic acid (CAS # 118-92-3) provide a calculated MOE > 100 for the repeated dose and developmental toxicity endpoints. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; phenylethyl anthranilate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; phenylethyl anthranilate 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.

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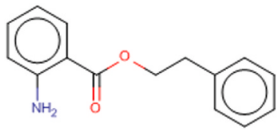
Name: Phenylethyl anthranilate
CAS Registry Number: 133-18-6



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

Phenylethyl anthranilate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from phenylethyl anthranilate and the read-across analog cinnamyl anthranilate (CAS # 87-29-6) show that phenylethyl anthranilate is not expected to be genotoxic. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class II material, and the exposure to phenylethyl anthranilate is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). Data on read-across analogs phenethyl alcohol (CAS # 60-12-8) and anthranilic acid (CAS # 118-92-3) provide a calculated MOE > 100 for the repeated dose and developmental toxicity endpoints. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; phenylethyl anthranilate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; phenylethyl anthranilate 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 expected to be genotoxic. (Zeiger et al., 1988; Wild et al., 1983)
Repeated Dose Toxicity: NOAEL = 385 mg/kg/day. Owston et al. (1981)
Developmental and Reproductive Toxicity: Developmental Toxicity NOAEL = 108 mg/kg/day. No reproductive toxicity NOAEL available. The exposure is below the TTC. RIFM (2010)
Skin Sensitization: Not a sensitization concern. Exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 2.61 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 409 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 2.35 mg/L (EPI Suite v4.1; US EPA, 2012a)
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: 2.35 mg/ (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00235 μg/L

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe Not Applicable: cleared at screening-level

1. Identification

1. **Chemical Name:** Phenylethyl anthranilate
2. **CAS Registry Number:** 133-18-6
3. **Synonyms:** Benzoic acid, 2-amino-, 2-phenylethyl ester; β-Phenethyl o-aminobenzoate; Phenethyl anthranilate; 2-Phenylethyl anthranilate; 2-Phenylethyl 2-aminobenzoate; Phenylethyl anthranilate
4. **Molecular Formula:** $C_{15}H_{15}NO_2$
5. **Molecular Weight:** 241.29
6. **RIFM Number:** 642

2. Physical data

1. **Boiling Point:** 374.21 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA)
3. **Log K_{OW}:** 4.46 (EPI Suite)
4. **Melting Point**: 40 °C (FMA), 128.76 °C (EPI Suite)
5. **Water Solubility:** 4.073 mg/L (EPI Suite)
6. **Specific Gravity:** 1.14000 to 1.14200 @ 25.00 °C*
7. **Vapor Pressure:** < 0.001 mm Hg 20 °C (FMA), 0.00000151 mm Hg @ 20 °C (EPI Suite v4.0), 3.2e-006 mm Hg @ 25 °C (EPI Suite)
8. **UV spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Fused, yellow-amber to white, colorless crystalline mass with almost no odor when pure. With impurities, odor is of neroli and grapefruit.

*http://www.thegoodscentscompany.com/data/rw1006421.html, retrieved 1/22/14.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0014% (RIFM, 2016)
3. **Inhalation Exposure*:** < 0.0001 mg/kg/day or 0.0000010 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0000016 mg/kg/day (RIFM, 2016)

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

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

4. Derivation of systemic absorption

1. **Dermal:** 77%

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

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II*	III	III

*See Appendix below for explanation.

2. Analogs Selected:
   a. **Genotoxicity:** Cinnamyl anthranilate (CAS # 87-29-6)
   b. **Repeated Dose Toxicity:** Phenethyl alcohol (CAS # 60-12-8) and anthranilic acid (CAS # 118-92-3)
   c. **Developmental and Reproductive Toxicity:** Phenethyl alcohol (CAS # 60-12-8) and anthranilic acid (CAS # 118-92-3)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

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

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

Phenylethyl anthranilate is not reported to occur in food by the VCF*.

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

8. Reach dossier

Pre-Registered for 2010; no dossier available as of 02/20/20.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, phenylethyl anthranilate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic potential of phenylethyl anthranilate was assessed in a bacterial reverse mutation assay conducted equivalent to OECD TG 471 using the modified preincubation method. *S. typhimurium* strains TA98, TA100, TA1535, TA97, and/or TA1537 were treated with cinnamyl anthranilate in dimethyl sulfoxide (DMSO) up to concentrations of 100 μg/plate (Zeiger et al., 1988). Under the conditions of the study, phenylethyl anthranilate was considered not mutagenic in bacteria.

There are no data assessing the clastogenicity of phenylethyl anthranilate; read-across was made to the analog cinnamyl anthranilate (CAS # 87-29-6; see section V). Cinnamyl anthranilate was assessed for clastogenic activity in an *in vivo* micronucleus study conducted similarly to OECD TG 474. Groups of 4 male and female NMRI mice were treated once with an intraperitoneal injection of cinnamyl anthranilate in olive oil at concentrations of 761, 1901, and 2533 mg/kg body weight and euthanized 30 h post injection (Wild et al., 1983). Under the conditions of the study, cinnamyl anthranilate was concluded to be negative for the induction of micronuclei in mice. Lack of clastogenic potential was observed in several studies performed by others including an *in vivo* micronucleus assay (Shelby et al., 1993), an *in vitro* sister chromatid exchange assay (Gulati et al., 1989), and an *in vitro* and several *in vivo* unscheduled DNA synthesis assays (Mirsalis et al., 1983, 1989; Steinmatz and Mirsalis, 1984). Additionally, weight of evidence can be provided from clastogenicity data on hydrolysis products 2-phenylethanol (CAS # 60-12-8) and anthranilic acid (CAS # 118-92-3). 2-Phenylethanol (CAS # 60-12-8) was negative in an *in vitro* chromosomal aberration assay conducted according to OECD 473/GLP (REACH: ECHA Dossier). Anthranilic acid was also negative in an *in vivo* micronucleus study conducted according to OECD 474/GLP (REACH: ECHA Dossier). Based on this data, cinnamyl anthranilate does not present a concern for clastogenic potential, and this can be extended to phenylethyl anthranilate.

Based on the data, phenylethyl anthranilate does not present a concern for genotoxicity.

Additional References: Dunkel et al. (1985); Tennant et al. (1987); McGregor et al. (1981); Zeiger et al. (1988); Dunkel and Simmon (1980); Gulati et al. (1989); Mirsalis et al. (1983); Palmer (1984); Foureman et al. (1994); Elmore and Fitzgerald (1990); Hatch et al. (1986); Mirsalis et al. (1989); Rudd et al. (1983); Dunkel et al. (1988); Lubet et al. (1990); Myhr and Caspary (1991); Matsuoka et al. (1996); Steinmetz and Mirsalis (1984); Suk et al. (1985); Shelby et al. (1993); Honma et al. (1999); Rossman et al. (1991); Yasunaga et al. (2004); Brauninger et al. (1993).

Literature Search and Risk Assessment Completed On: 01/17/14.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for phenylethyl anthranilate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on phenylethyl anthranilate. Phenethyl anthranilate is expected to hydrolyze to phenethyl alcohol (CAS # 60-12-8; see section V) and anthranilic acid (CAS # 64-18-6; see section V). Phenethyl alcohol was administered at 0.25, 0.5, 1.0, and 2.0 mL/kg/day (250, 500, 1000, and 2000 mg/kg/day) for 90 days in open application to the shaved dorsa of 15 Sprague Dawley rats per sex per dose. The NOAEL was determined to be 0.5 mL/kg/day (500 mg/kg/day) based on reduction in body weight and bodyweight gains among the higher dose group animals (Owston et al., 1981). In another study, Fischer 344 rats or B6C3F1 mice, when treated with metabolite anthranilic acid administered via diet at doses up to 30000 ppm and 50000 ppm, respectively, for a period of 2 years, showed no evidence of carcinogenicity that could be related to treatment with anthranilic acid (NCI, 1978). The dietary dose was equivalent to 3000 mg/kg/day and 7500 mg/kg/day in rats and mice, respectively (as per the conversion factors for old rats available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives). The NOAEL of 500 mg/kg/day for phenethyl alcohol was considered for the repeated dose toxicity endpoint. To account for bioavailability following dermal application, data from a rat *in vivo* study (RIFM, 2013b; see Section IV) was used to revise the NOAEL of 500 mg/kg/day to reflect the systemic dose. At a dermal penetration of 77% of applied dose, the revised phenethyl alcohol toxicity NOAEL from the dermal study is 385 mg/kg/day.

Therefore, the phenylethyl anthranilate MOE for the repeated dose toxicity endpoint can be calculated by dividing the phenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to phenylethyl anthranilate, 385/0.0000016 or 240625000.

In addition, the total systemic exposure to phenylethyl anthranilate (0.0016 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: Caldwell et al. (1985); Caldwell et al. (1988); Bronaugh and Stewart (1984); Bronaugh and Stewart, 1986; Hotchkiss (1998); Verrett et al., 1980; Hagan et al., 1967; Bar and Griepentrog (1967); OECD QSAR Toolbox (Dow Chemical, 1967 from MUNRO database); Schafer and Bowles (1985); Clark et al. (1980); Cutting et al. (1966); RIFM, 1974; Grundschober (1977); Yamaori et al. (2005); NCI, 1978; Ekman and Strombeck (1949).

Literature Search and Risk Assessment Completed On: 09/14/16.

10.1.3. Developmental and reproductive toxicity

The MOE for phenylethyl anthranilate is adequate for the developmental toxicity endpoint at the current level of use.

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

10.1.3.1. Risk assessment. There are no developmental and reproductive toxicity data on phenylethyl anthranilate. Phenethyl anthranilate is expected to hydrolyze to phenethyl alcohol (CAS # 60-12-8; see section V) and anthranilic acid (CAS # 64-18-6; see section V). A dietary developmental toxicity study was conducted on groups of 28 pregnant rats that were fed diets containing phenethyl alcohol at doses of 0, 1000, 3000, or 10000 ppm, equivalent to 0, 83, 266, or 799 mg/kg/day according to calculated food intake from gestation days (GDs) 6–15. There were no maternal or fetal developmental toxicity effects reported among treated animals. Thus, the NOAEL for maternal and developmental toxicity was determined to be 10000 ppm or 799 mg/kg/day, the highest dose tested RIFM (2013a). In another study, a dermal developmental toxicity study was conducted on groups of 25–35 pregnant female rats that were administered phenethyl alcohol at doses of 0, 140, 430, or 1400 mg/kg/day from gestation days 6–15. There was significant maternal toxicity reported among the high-dose animals. Thus, the maternal toxicity NOAEL was determined to be 430 mg/kg/day. A dose-related increase in skeletal abnormalities was reported among the animals of the mid- and high-dose group animals; thus, the NOAEL for developmental toxicity was determined to be 140 mg/kg/day (RIFM, 2013a).

Another dermal developmental toxicity study was conducted on

phenethyl alcohol at doses of 0, 70, 140, 280, 430, and 700 mg/kg/day. Groups of 10 rats/sex/group were treated with PEA from GDs 6–15. Fetal effects included a dose-dependent decrease in fetal body weights for litters of the 140 mg/kg/day and higher dose groups. Dosages as high as 700 mg/kg/day did not adversely affect average litter sizes, numbers of implantations, live fetuses, or post-implantation loss. Thus, the NOAEL for developmental toxicity was determined to be 70 mg/kg/day based on decreases in body weights of litters among the higher dose groups (RIFM, 2013a). Another study was conducted to determine the reversibility of skeletal alterations (e.g., rudimentary cervical ribs and vertebral irregularities) and delays in skeletal ossification following exposure of pregnant rats to the test material during the gestation period. Any safety concerns relating to human health were also evaluated. Dosages of 0 (water) 140, 430, or 1400 mg/kg/day PEA were percutaneously administered once daily on GDs 7–20. Twenty rats per dosage group were caesarean-sectioned on GD 21. The remaining 20 rats per dosage group were allowed to deliver naturally; the dams and pups were euthanized on Postpartum Day (PPD) 21. The maternal toxicity NOAEL was determined to be 430 mg/kg/day based on increased incidences of altered clinical observations and mortality among the high-dose group animals. The NOAEL for developmental toxicity was determined to be 140 mg/kg/day based on increased incidences of fetal skeletal ossifications among the mid- and high-dose group animals as well as gross, soft tissue, and skeletal alterations among the high-dose group animals (RIFM, 2010). There are no developmental toxicity data on metabolite anthranilic acid. The most conservative NOAEL of 140 mg/kg/day from the dermal studies on phenethyl alcohol was selected for the developmental toxicity endpoint. To account for bioavailability following dermal application, data from a rat *in vivo* study (RIFM, 2013b; see Section IV) was used to revise the NOAEL of 140 mg/kg/day to reflect the systemic dose. At a dermal penetration of 77% of applied dose, the revised phenethyl alcohol toxicity NOAEL from the dermal study is 108 mg/kg/day.

Therefore, the phenethyl anthranilate MOE for the developmental toxicity endpoint can be calculated by dividing the phenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to phenethyl formate, 108/0.0000016 or 67500000.

There are no reproductive toxicity data on phenylethyl anthranilate or any of the read-across materials. The total systemic exposure to phenylethyl anthranilate (0.0016 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: Caldwell et al. (1985); Caldwell et al. (1988); Bronaugh and Stewart (1984); Bronaugh and Stewart (1986); Hotchkiss (1998); Verrett et al. (1980); Hagan et al. (1967); Bar and Griepentrog (1967); OECD QSAR Toolbox (Dow Chemical, 1967 from MUNRO database); Schafer and Bowles (1985); Clark et al. (1980); Cutting et al. (1966); RIFM, 1974; Grundschober (1977); Yamaori et al. (2005); NCI, 1978; Ekman and Strombeck (1949).

Literature Search and Risk Assessment Completed On: 09/14/16.

10.1.4. Skin sensitization

Based on the available data and application of the DST, phenylethyl anthranilate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data and application of the DST, phenylethyl anthranilate does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD Toolbox v3.1). In a human maximization test, no reactions to phenylethyl anthranilate were observed (RIFM, 1975). The reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2. The current 95th percentile dermal exposure is below the DST for non-reactive materials when evaluated in all QRA categories.

Table 1
Maximum acceptable concentrations for phenylethyl anthranilate that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Examples of Product Type	Calculated QRA
1	Lip Products	0.026%
2	Deodorant/Antiperspirant	0.033%
3	Hydroalc., Shaved Skin	0.136%
4	Hydroalc., Unshaved Skin	0.407%
5	Women Facial Cream	0.214%
6	Mouthwash	0.652%
7	Intimate Wipes	0.068%
8	Hair Styling Aids Non-Spray	0.91%
9	Conditioners, Rinse-off	4.50%
10	Hard Surface Cleaners	2.5%
11	Candle (Non-Skin/Incidental Skin)	Not Restricted

Note.
[a] For a description of the categories, refer to the QRA Informational Booklet. (www.rifm.org/doc/QRAInfoJuly2011.pdf).

Phenylethyl anthranilate does not present a concern for skin sensitization (See Table 1).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/27/16.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, phenylethyl anthranilate would not be expected to present a concern for phototoxicity or photoallergenicity.

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

10.1.5.2. Key studies. There are no studies available on phenylethyl anthranilate in experimental models.

10.1.5.2.1. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/07/16.

10.1.5.3. Local respiratory toxicity. The MOE could not be calculated due to a lack of appropriate data. The exposure level of phenylethyl anthranilate is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.6. Risk assessment

There are no inhalation data available on phenylethyl anthranilate. Based on the Creme RIFM model, the inhalation exposure is 0.0000010 mg/day. This exposure is 470,000 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/07/16.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of phenylethyl anthranilate 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, phenylethyl anthranilate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.1 identified phenylethyl anthranilate as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on the current Volume of Use (2011), phenylethyl anthranilate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Biodegradation. No data available.

10.2.1.2.1. Ecotoxicity. No data available.

10.2.1.2.2. Other available data. Phenylethyl anthranilate has been pre-registered for REACH with no additional data at this time.

10.2.2. Risk assessment refinement

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>2.35</u>			1,000,000	0.00235	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.46	4.46
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	< **1**	< **1**

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

The RIFM PNEC is 0.00235 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: 01/17/14.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&

sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.
*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 02/20/20.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111470.

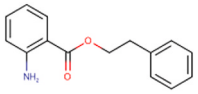
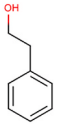
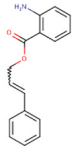
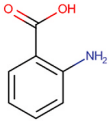
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2012).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target material	Read-across material		
Principal Name	Phenylethyl anthranilate	Phenethyl alcohol	Cinnamyl anthranilate	Anthranilic acid
CAS No.	133-18-6	60-12-8	87-29-6	118-92-3
Structure				
Similarity (Tanimoto score)[1]		NA	0.51	NA
Read-across endpoint		• Repeated dose • Developmental	• Genotoxicity	• Repeated dose • Developmetnal
Molecular Formula	$C_{15}H_{15}NO_2$	$C_8H_{10}O$	$C_{16}H_{15}NO_2$	$C_7H_7NO_2$
Molecular Weight	241.29	122.17	253.3	139.15
Melting Point (°C, EPI Suite)	128.76	5.81	136.73	94.08
Boiling Point (°C, EPI Suite)	374.21	224.85	389.38	307.70
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.000427	0.0243	0.000926	0.0105
Log Kow (KOWWIN v1.68 in EPI Suite)	4.46	1.36	4.74	1.21
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.073	2.199E+004	2.031	3500
J_{max} (μg/cm^2/h, SAM)	4.41	355.140	1.140	29.603
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.31E-009	2.89E-007	7.21E-010	3.83E-011
Genotoxicity				
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found		• No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition • SN1, Nitrenium ion formation		• SN1, Nitrenium Ion formation	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Carcinogen (moderate reliability)		• Carcinogen (Experimental value)	
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found		• No alert found	

***In vitro* Mutagenicity (Ames test) alerts by ISS**	• Primary aromatic amine, hydroxyl amine and its derived esters		• Primary aromatic amine, hydroxyl amine and its derived esters	
***In vivo* mutagenicity (Micronucleus) alerts by ISS**	• Primary aromatic amine, hydroxyl amine and derived esters • H-acceptor-path3-H-acceptor		• Primary aromatic amine, hydroxyl amine and derived esters • H-acceptor-path3-H-acceptor	
Oncologic Classification	• Aromatic amine type compound		• Aromatic amine type compound	
Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized	• Not categorized		• Not categorized
Reproductive and developmental toxicity				
ER Binding by OECD QSAR Tool Box (3.4)	• Strong binder NH_2 group	• Non-binder, without OH and NH_2 group		• Weak binder NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (moderate reliability)	• Toxicant (good reliability)		• Toxicant (low reliability)
Metabolism				
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	• NA	See Supplemental Data 2	• NA

Summary

There are insufficient toxicity data on phenylethyl anthranilate (CAS # 133-18-6). Hence, *in silico* evaluation was conducted by determining suitable read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, suitable analogs cinnamyl anthranilate (CAS # 87-29-6), phenethyl alcohol (CAS # 60-12-8), and anthranilic acid (CAS # 118-92-3) were identified as read-across materials with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target substance was not considered for the risk assessment, and therefore, metabolism data were not reviewed except where it may pertain in specific endpoint sections above. Metabolism of the target substance phenethyl anthranilate (CAS # 133-18-6) was predicted using the rat liver S9 metabolism simulator (OECD QSAR Toolbox v3.4) (See Appendix). The target material is predicted to metabolize to phenethyl alcohol (CAS # 60-12-8) and anthranilic acid (CAS # 118-92-3) in the first step with 0.92 pre-calculated probability. Hence, phenethyl alcohol and anthranilic acid can be use as read-across for the target material. Read-across analogs were out of domain for the *in vivo* rat and out of domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden and a justification is provided.

Conclusions

- Cinnamyl anthranilate (CAS # 87-29-6) was used as structurally similar read-across analog for the target material phenylethyl anthranilate (CAS # 133-18-6) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of anthranilates.
  - o The target substance and the read-across analog have the methyl anthranilate fragment common among them.
  - o The key difference between the target substance and the read-across analog is that the target has an ethyl phenyl fragment while the read-across analog has a methyl group substituted on anthranilate. This structure difference between the target substance and the read-across analog does not raise additional structural alerts, so the structure differences are toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o The target substance and the read-across analog have several genotoxicity alerts including carcinogen categorization by the ISS model. The data described in the genotoxicity section above show that the read-across analog does not pose a concern for genetic toxicity. Therefore the alerts will be superseded by the availability of the data.
  - o In spite of a structural alert due to the presence of a substituted amino group (Ashby et al., 1988), the presence of an ortho carboxylic group might hinder the metabolic activation of the adjacent nitrogen substituent (Benigni et al., 2000).
  - o The target substance and the read-across analog are expected to be metabolized similarly as shown by metabolism simulator.
  - o The structural differences between the target substance and the read-across analog are deemed to be toxicologically insignificant.
- Phenethyl alcohol (CAS # 60-12-8) and anthranilic acid (CAS # 118-92-3) are used as read-across analogs for phenethyl anthranilate (CAS # 133-18-6) for the reproductive and developmental toxicity and repeated dose toxicity endpoints.
  - o The read-across materials are major metabolites or are analogs of the major metabolites of the target.
  - o The target substance is an ester formed from the read-across analog alcohol and the read-across analog acid.
  - o Structural differences between the target substance and the read-across analog are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analog. Therefore, the toxicity profile of the target is expected to be that of metabolites.
  - o The target substance and the read-across analog are shown to have an ER binding alert. ER Binding is a molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity. It shows that the read-across analog is predicted to have similar reactivity compared to the target substance. The data described in the reproductive and developmental toxicity section show that the read-across analog has an adequate margin of exposure at the current level of use. Therefore, the alert will be superseded by the availability of data.
  - o The target substance and the read-across analogs are predicted to be toxicants by the CAESAR model for developmental toxicity. The data described in the developmental toxicity section above show that the read-across analogs have adequate margins of exposure at the current levels of use. Therefore, the alert will be superseded by the availability of the data.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree.

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? Yes
Q27. Rings with substituents? Yes
Q28. More than one aromatic ring? No
Q30. Aromatic ring with complex substituents? Yes
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No
Q22. Common component of food? Yes, Intermediate (Class II)

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