Food and Chemical Toxicology 144 (2020) 111531

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, β-naphthyl anthranilate, CAS Registry Number 63449-68-3

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ARTICLE INFO

Keywords:
Genotoxicity
Repeated dose, developmental, and reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

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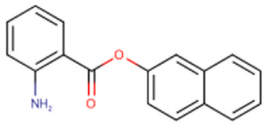
https://doi.org/10.1016/j.fct.2020.111531
Received 6 August 2019; Received in revised form 12 May 2020; Accepted 11 June 2020
Available online 05 July 2020

Version: 011519. This version replaces any previous versions.
Name: β-Naphthyl anthranilate CAS Registry Number: 63449-68-3



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., 2015a, 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, 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.
β-Naphthyl anthranilate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs β-naphthol (CAS # 135-19-3) and anthranilic acid (CAS # 118-92-3) show that β-naphthyl anthranilate is not expected to be genotoxic. Data on read-across analogs β-naphthol (CAS # 135-19-3) and anthranilic acid (CAS # 118-92-3) provide a calculated MOE > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class III material, and the exposure to β-naphthyl anthranilate is below the TTC (0.0015 mg/kg/day and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the DST for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; β-naphthyl anthranilate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; β-naphthyl 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. (ECHA Reach Dossier: 2-Naphthol; ECHA, 2018)
Repeated Dose Toxicity: NOAEL = 1 mg/kg/day. (OECD SIDS: 2-Naphthol, 2002)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a sensitization concern; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence:
Screening-level: 2.6 (BIOWIN 3) (EPI Suite v.4.11; US EPA 2012a)

Bioaccumulation:	
Screening-level: 549 L/kg	(EPI Suite v.4.11; US EPA 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 1.94 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: 1.94 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.00194 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** β-Naphthyl anthranilate
2. **CAS Registry Number:** 63449-68-3
3. **Synonyms:** 2-Naphthalenol, 2-aminobenzoyl ester; 2-Naphthyl o-aminobenzoate; 2-Naphthyl anthranilate; 2-Naphthyl 2-aminobenzoate; β-Naphthyl anthranilate
4. **Molecular Formula:** $C_{17}H_{13}NO_2$
5. **Molecular Weight:** 263.29
6. **RIFM Number:** 6818
7. **Stereochemistry:** No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 421.9 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA Database)
3. **Log K_{OW}:** 4.66 (EPI Suite)
4. **Melting Point**: 160.6 °C (EPI Suite)
5. **Water Solubility:** 2.1 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 4.31E-08 mm Hg @ 20 °C (EPI Suite v4.0), 9.86e-008 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Pale straw colored or almost colorless liquid. Orange blossom type derivatives (Arctander, Volume II, 1969)

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00094% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0000001 mg/kg/day or 0.0000051 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0000037 mg/kg/day (RIFM, 2016)

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High* (Expert Judgment)

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

*Due to potential discrepancies with 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 (Cramer et al., 1978). See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** β-naphthol (CAS # 135-19-3); anthranilic acid (CAS # 118-92-3)
   b. **Repeated Dose Toxicity:** β-naphthol (CAS # 135-19-3); anthranilic acid (CAS # 118-92-3)
   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: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment. **Additional References**: None.

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

β-Naphthyl anthranilate is not reported to occur in foods 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. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 01/15/19.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, β-naphthyl anthranilate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. β-naphthyl anthranilate was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: < 80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2015). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic and clastogenic activity of β-naphthyl anthranilate; however, read-across can be made to the hydrolysis products of the target ester, β-naphthol (CAS # 135-19-3) and anthranilic acid (CAS # 118-92-3) (see Section V).

The mutagenic activity of β-naphthol has been evaluated in several bacterial reverse mutation assays conducted according to OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with β-naphthol. In another bacterial reverse mutation assay *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with β-naphthol. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2018). Under the conditions of the study, β-naphthol was not mutagenic in the Ames test, and this can be extended to β-naphthyl anthranilate.

The mutagenic activity of anthranilic acid has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with anthranilic acid in ethanol at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2013). Under the conditions of the study, anthranilic acid was not mutagenic in the Ames test, and this can be extended to β-naphthyl anthranilate.

The clastogenic activity of β-naphthol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in methylcellulose solution via oral gavage to groups of male and female BDF1 mice. Doses of 62.5, 125, or 250 mg/kg body weight were administered. Mice from each dose level were euthanized at 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2018). Under the conditions of the study, β-naphthol was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to β-naphthyl anthranilate.

The clastogenic activity of anthranilic acid was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in sodium carboxymethyl cellulose via oral gavage to groups of male and female ICR mice. Doses of 750, 1500, and 3000 mg/kg body weight were administered to males and doses of 600, 1200, 2400 mg/kg body weight were administered to females. Mice from each dose level were euthanized at 24 and 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2013). Under the conditions of the study, anthranilic acid was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to β-naphthyl anthranilate.

Based on the data available, β-naphthol and anthranilic acid do not present a concern for genotoxic potential, and this can be extended to β-naphthyl anthranilate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/03/19.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for β-naphthyl anthranilate is sufficient 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 β-naphthyl anthranilate. However, target material β-naphthyl anthranilate is expected to hydrolyze into β-naphthol (CAS # 135-19-3; see section V) and anthranilic acid (CAS # 118-92-3; see section V). There are sufficient repeated dose toxicity data on both β-naphthol and anthranilic acid.

Hydrolysis product β-naphthol has been assessed under the OECD Screening Information Dataset (SIDS) program in Oct 2002 and was considered a chemical of low priority for further work based on its low hazard potential (OECD SIDS: 2-naphthol, 2002). Repeated dose toxicity data available on β-naphthol include OECD 407 and 415 studies.

During the OECD 407 study, the test material β-naphthol was administered to groups of 5 Sprague Dawley rats/sex/dose via gavage at doses of 0 (CMC), 50, 150, and 450 mg/kg/day. An additional 4 weeks recovery group received either vehicle or 450 mg/kg/day of β-naphthol. Besides alterations reported in clinical chemistry parameters indicating altered kidney function among mid- and high-dose group animals, there was a decrease in adrenal weights, both absolute and relative, among all treated animals. Although there were no macroscopic or microscopic changes in any organs in treated animals, the LOAEL was considered to be 50 mg/kg/day based on decrease in adrenal weights among treated animals.

In the OECD 415 study, test material β-naphthol was administered to groups of 25 Sprague Dawley rats/sex/dose through oral gavage at doses of 0 (0.5% CMC), 10, 40, or 160 mg/kg/day. The males were administered test material for approximately 98 days (starting from 10 weeks prior to mating until necropsy). The females were administered the test material starting 2 weeks prior to mating until lactation day 20. Males in particular showed signs of transient salivation after dosing. Locomotor activity decreased in animals at doses ≥40 mg/kg/day. Males receiving 40 mg/kg/day dose showed transient signs of complete eye closure and nasal discharge. High-dose group males showed transient lacrimation after dosing. There were no alterations due to treatment in body weight and food consumption among treated males. Thickened forestomach mucosa due to squamous cell hyperplasia was reported in mid- and high-dose group males. Low-dose group males showed no signs of treatment-related alterations throughout the study duration. Females in the mid- and high-dose groups were reported to have nasal discharge along with reduced locomotor activity. Food consumption in females in the mid- and high-dose groups was significantly reduced. The LOEL for systemic toxicity among males was considered to be 10 mg/kg/day based on incidences of salivation observed among all treatment groups, and the NOAEL for female systemic toxicity was considered to be 10 mg/kg/day, based on reduced food consumption and locomotor activity in the higher-dose group.

Since the animals were treated for at least 90 days during the OECD 415 study, this study was considered for the derivation of a NOAEL for the repeated dose toxicity endpoint. The OECD 415 study derived a LOAEL of 10 mg/kg/day due to transient effects of salivation observed among all treated males. Hence an uncertainty factor of 10 was used to derive a NOAEL from the reported LOAEL. Therefore, the NOAEL for the OECD 415 study was considered to be 10/10, or 1 mg/kg/day.

For metabolite anthranilic acid, a study was conducted with anthranilic acid administered in the diet for 2 years at doses up to

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

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	NRU[b]
2	Products applied to the axillae	0.0015%	1.7×10^{-4}%
3	Products applied to the face using fingertips	0.029%	4.4×10^{-8}%
4	Fine fragrance products	0.027%	0.0010%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	3.7×10^{-5}%
6	Products with oral and lip exposure	0.016%	NRU[b]
7	Products applied to the hair with some hand contact	0.056%	9.0×10^{-6}%
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	1.2×10^{-4}%
10	Household care products with mostly hand contact	0.19%	8.6×10^{-6}%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	1.1×10^{-4}%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

30000 ppm and 50000 ppm in Fischer 344 rats and B6C3F1 mice, respectively. The study did not report any evidence of carcinogenicity related to 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 authors of the study concluded that anthranilic acid was not carcinogenic to rats or mice during the duration of the bioassay.

Overall, from the available data on hydrolysis products β-naphthol and anthranilic acid, the most conservative NOAEL available for the repeated dose toxicity endpoint was 1 mg/kg/day as determined from the OECD 415 study on β-naphthol. Thus, this conservative NOAEL of 1 mg/kg/day from the OECD 415 study on β-naphthol can be the NOAEL for the repeated dose toxicity endpoint for the safety assessment on β-Naphthyl anthranilate.

Therefore, the β-naphthyl anthranilate MOE is equal to the β-naphthol NOAEL in mg/kg/day divided by the total systemic exposure to β-naphthyl anthranilate, 1/0.0000037 or 270270.

In addition, the total systemic exposure to β-Naphthyl anthranilate (0.0037 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/02/19.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on β-naphthyl anthranilate or on any read-across materials. The total systemic exposure to β-naphthyl anthranilate is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on β-naphthyl anthranilate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to β-naphthyl anthranilate (0.0037 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/14/18.

10.1.4. Skin sensitization

Based on the existing data and the application of DST, β-naphthyl anthranilate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for β-naphthyl anthranilate. Acting conservatively, due to the absence of data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for β-naphthyl anthranilate that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/12/19.

10.1.5. Phototoxicity/photoallergenicity

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

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/20/18.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for β-naphthyl anthranilate is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on β-naphthyl anthranilate. Based on the Creme RIFM Model, the inhalation exposure is 0.0000051 mg/day. This exposure is 92157 times lower than the Cramer Class III TTC value of 0.47 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: None.

Literature Search and Risk Assessment Completed On: 12/12/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of β-naphthyl anthranilate 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 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, β-naphthyl 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 v4.11 (US EPA, 2012a) identified β-naphthyl anthranilate as not 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

10.2.2. Risk assessment

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

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. β-naphthyl anthranilate has been pre-registered for REACH with no additional data at this time.

10.2.3. 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>1.94</u>			1000000	0.00194	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.6	4.6
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	< **1**	< **1**

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

The RIFM PNEC is 0.00194 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 12/12/18.

11. 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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 05/31/19.

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.2020.111531.

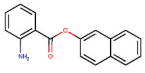
Appendix

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, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target 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, 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).
- 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).

	Target Material	Read-across Material	Read-across Material
Principal Name	β-Naphthyl anthranilate	2-Naphthol	Benzoic acid, 2-amino- (synonym: anthranilic acid)
CAS No.	63449-68-3	135-19-3	118-92-3
Structure			
Similarity (Tanimoto Score)		0.26	0.47
Read-across Endpoint		• Genotoxicity • Repeated Dose Toxicity	• Genotoxicity • Repeated Dose Toxicity
Molecular Formula	$C_{17}H_{13}NO_2$	$C_{10}H_8O$	$C_7H_7NO_2$
Molecular Weight	263.29	144.17	137.13
Melting Point (°C, EPI Suite)	160.60	67.72	145
Boiling Point (°C, EPI Suite)	421.90	282.86	307.70
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.31E-005	4.27E-002	145
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.66	2.70	1.21
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.1	1244.5	3500
J_{max} (μg/cm^2/h, SAM)	0.491	84.08	29.60
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.49E-005	2.78E-003	3.88E-006

Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found	• Radical|Radical ≫ Radical mechanism via ROS formation (indirect)|Radical ≫ Radical mechanism via ROS formation (indirect) ≫ Single-Ring Substituted Primary Aromatic Amines|SN1|SN1 ≫ Nucleophilic attack after nitrenium ion formation|SN1 ≫ Nucleophilic attack after nitrenium ion formation ≫ Single-Ring Substituted Primary Aromatic Amines
DNA Binding (OECD QSAR Toolbox v4.2)	• SN1|SN1 ≫ Nitrenium Ion formation|SN1 ≫ Nitrenium Ion formation ≫ Primary aromatic amine	• No alert found	• No alert found
Carcinogenicity (ISS)	• Carcinogen (good reliability)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (experimental value)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• Primary aromatic amine, hydroxyl amine and its derived esters	• No alert found	• No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• H-acceptor-path3-H-acceptor|Primary aromatic amine, hydroxyl amine and its derived esters	• No alert found	• H-acceptor-path3-H-acceptor
Oncologic Classification	• Aromatic Amine Type Compounds	• Phenol Type Compounds	• Aromatic Amine Type Compounds
Repeated Dose Toxicity			
Repeated Dose (HESS)	• 2-Amino-4,5-diphenyl thiazole (Renal toxicity) Alert • 3-Methylcholantrene (Hepatotoxicity) Alert • Alpha-Naphthyl-isothiocyanate (Hepatotoxicity) Alert • Anthraquinone (Renal toxicity) Alert • B-Naphthylisothiocyanate (Hepatotoxicity) Alert • Bromfenac (Hepatotoxicity) Alert • Carbamazepine (Hepatotoxicity) Alert • Carbamazepine (Renal Toxicity) Alert • Tamoxifen (Hepatotoxicity) Alert	• 2-Acetylaminofluorene (Hepatotoxicity) Alert • 2-Amino-4,5-diphenyl thiazole (Renal toxicity) Alert • 3-Methylcholantrene (Hepatotoxicity) Alert • Acetaminophen (Hepatotoxicity) Alert • Acetaminophen (Renal toxicity) Alert • Alpha-Naphthyl-isothiocyanate (Hepatotoxicity) Alert • B-Naphthylisothiocyanate (Hepatotoxicity) Alert • Carbamazepine (Hepatotoxicity) Alert • Carbamazepine (Renal Toxicity) Alert	• Mefenamic Acid (Hepatotoxicity) Alert • Menadione (Hepatotoxicity) Alert
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• No metabolites	• No metabolites

Summary

There are insufficient toxicity data on β-naphthyl anthranilate (CAS # 63449-68-3). 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, 2-naphthol (CAS # 135-19-3) and benzoic acid, 2-amino- (CAS # 118-92-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Read-across alcohol 2-naphthol (CAS # 135-19-3) and read-across acid benzoic acid, 2-amino- (CAS # 118-92-3) are used as read-across analogs for target ester β-naphthyl anthranilate (CAS # 63449-68-3) for the genotoxicity and repeated dose toxicity endpoints.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - o Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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? Yes
Q29 Readily hydrolyzed? Yes
Q33 Has sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? No, Class III (Class high)

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