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Short review

RIFM Fragrance Ingredient Safety Assessment, Butyl anthranilate, CAS Registry Number 7756-96-9

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- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe (not reported): not applicable; cleared at screening level

1. Identification

1. **Chemical Name:** Butyl anthranilate
2. **CAS Registry Number:** 7756-96-9
3. **Synonyms:** Benzoic acid, 2-amino-, butyl ester; Butyl 2-aminobenzoate; Butyl o-aminobenzoate; n-Butyl anthranilate; Butyl anthranilate
4. **Molecular Formula:** $C_{11}H_{15}NO_2$
5. **Molecular Weight**: 193.25
6. **RIFM Number:** 574

2. Physical data

1. **Boiling Point:** 148 °C @ 0.3 mm Hg [FMA database], 309.84 °C [EPI Suite]
2. **Flash Point:** 230 °F; CC [FMA database]
3. **Log K_{OW}:** 3.74 [EPI Suite]
4. **Melting Point:** 86.18 °C [EPI Suite]

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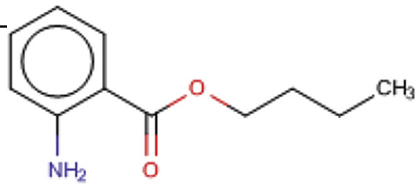
0278-6915/

Version: 041817. This version replaces any previous versions.

Name: Butyl anthranilate
CAS Registry Number: 7756-96-9



Abbreviation 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; Safford et al., 2015; 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
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
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/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 under the limits 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 reviews 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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (*i.e.*, 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 end-point 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the target material and the read across analog methyl anthranilate (CAS# 134-20-3) show that this material is not genotoxic. Data from the read across analog methyl anthranilate (CAS # 134-20-3) show that this material does not have skin sensitization potential and provided a MOE > 100 for the repeated dose and developmental toxicity endpoints. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class II material (0.009 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra and data on the read across analog ethyl anthranilate (CAS # 87-25-2). The environmental endpoints were evaluated and this material was not found to be a PBT; PEC/PNEC (North America and Europe) < 1 (cleared at screening level).

Human Health Safety Assessment
Genotoxicity: Not genotoxic (Zeiger et al., 1987; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day (Hagan et al., 1967)
Reproductive Toxicity: Developmental: NOAEL = 768.4 mg/kg/day and **Fertility:** No NOAEL available. Exposure is below the TTC. (RIFM, 2012)
Skin Sensitization: Not sensitizing (RIFM, 2007; RIFM, 1973; 1974; RIFM, 1974; RIFM, 1964)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB; RIFM, 1976a; RIFM, 1976b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:

(*continued on next page*)

(*continued*)

Persistence: Screening Level: 3.07 (Biowin 3) (EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 136 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 7.985 mg/L (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 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 7.985 mg/L (Salvito et al., 2002)
RIFM PNEC is: 0.007985 μg/L

5. **Water Solubility:** 30.4 mg/L [EPI Suite]
6. **Specific Gravity:** 1.07 [FMA database]
7. **Vapor Pressure:** 0.000156 mmHg @ 20 °C [EPI Suite 4.0], 0.000299 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} cm^{-1})
9. **Appearance/Organoleptic:** A colorless or very pale straw-colored liquid with a mild, sweet-fruity-floral odor, including the inevitable orange blossom theme.

3. Exposure

1. Volume of Use (worldwide band): <0.1 metric tons per year (IFRA , 2011)
2. 95th Percentile Concentration in Rinse off Conditioners: 0.00050% (No reported use in Hydroalcoholics) (RIFM, 2016)
3. Inhalation Exposure*: 0.000021 mg/kg/day or 0.0015 mg/day (RIFM, 2016)
4. Total Systemic Exposure**: 0.000028 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 and Safford et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

*See Appendix below for explanation.

2. Analogs Selected:
   a. **Genotoxicity:** methyl anthranilate (CAS# 134-20-3)
   b. **Repeated Dose Toxicity:** methyl anthranilate (CAS# 134-20-3)
   c. **Reproductive Toxicity:** methyl anthranilate (CAS# 134-20-3)
   d. **Skin Sensitization:** methyl anthranilate (CAS # 134-20-3)
   e. **Phototoxicity/Photoallergenicity:** Ethyl anthranilate (CAS # 87-25-2)
   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)

Butyl 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, contains information on published volatile compounds which 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 4/18/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.2. Risk assessment

The mutagenic activity of butyl anthranilate (CAS # 7756-96-9) has been evaluated in a bacterial reverse mutation assay using the

preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 were treated with butyl anthranilate in DMSO (dimethyl sulfoxide) at concentrations up to 280 or 50 μg/plate in presence and absence of metabolic activation, respectively. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (Zeiger et al., 1987). Under the conditions of the study, butyl anthranilate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of butyl anthranilate however, read across can be made to methyl anthranilate (CAS # 134-20-3; see Section 5). The clastogenic activity of methyl anthranilate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with methyl anthranilate in DMSO (dimethyl sulfoxide) at concentrations up to 1512 μg/mL in the presence and absence of metabolic activation (S9) at the 3-h and 24-h time points. Methyl anthranilate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2015). Under the conditions of the study, methyl anthranilate was considered to be non-clastogenic in the *in vitro* micronucleus test and this can be extended to butyl anthranilate.

Based on the data available, butyl anthranilate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/12/2016.

10.1.3. Repeated dose toxicity

The margin of exposure for butyl anthranilate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

There are no repeated dose toxicity data on butyl anthranilate. There are sufficient repeated dose toxicity data on read across material methyl anthranilate (CAS# 134-20-3; see section 5). A dietary 90-day subchronic toxicity study was conducted in rats. Groups of 10 weanling Osborne-Mendel rats per sex were administered test material, methyl anthranilate in the diet for 13 weeks at dose levels of 0, 1000 or 10000 ppm (equivalent to 0, 50 or 500 mg/kg/day). There were no test material-related adverse effects reported up to the highest dose tested. Thus, the NOAEL for the repeated dose toxicity endpoint was determined to be 10000 ppm or 500 mg/kg/day (Hagan et al., 1967; data also available in Bar and Griepentrog, 1967). Therefore, the butyl anthranilate MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl anthranilate NOAEL in mg/kg/day by the total systemic exposure to butyl anthranilate, 500/0.000028 or 17857143.

In addition, the total systemic exposure to butyl anthranilate (0.028 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/14/2016.

10.1.5. Reproductive toxicity

The margin of exposure for butyl anthranilate is adequate for the developmental toxicity endpoint at the current level of use.

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

10.1.6. Risk assessment

There are no developmental toxicity data on butyl anthranilate. Read across material, methyl anthranilate (CAS# 134-20-3; see section 5 has sufficient developmental toxicity data. An OECD 414 dietary developmental toxicity study was conducted in rats (RIFM, 2012). Presumed pregnant rats (25/dose) were fed methyl anthranilate in the diet at dose levels of 0, 1000, 5000 or 10000 ppm (average daily consumption of 0, 80.4, 389.9 or 768.4 mg/kg/day) on Days 6 through 20 of presumed gestation. The adult animals among the 1000, 5000 and 10000 ppm dose groups had reduced body weight gains and animals among the 5000 and 10000 ppm dose group had reduced food consumption. However, there were no developmental toxicity findings reported among the pups up to the highest dose tested. The NOAEL for maternal toxicity was determined to be 1000 ppm or 80.4 mg/kg/day and the NOAEL for developmental toxicity was determined to be 10000 ppm or 786.4 mg/kg/day, the highest dosage tested. Therefore, the butyl anthranilate MOE for the developmental toxicity endpoint can be calculated by dividing the methyl anthranilate NOAEL in mg/kg/day by the total systemic exposure to butyl anthranilate, 768.4/0.000028 or 27442857.

In addition, the total systemic exposure to butyl anthranilate (0.028 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

There are no fertility data on butyl anthranilate or any of the read across materials. The total systemic exposure to butyl anthranilate (0.028 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the fertility endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/14/2016.

10.1.7. Skin sensitization

Based on the existing material specific data and read across to methyl anthranilate (CAS # 134-20-3), butyl anthranilate does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the available data and read across material methyl anthranilate, (CAS # 134-20-3; see Section 5), butyl anthranilate does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In guinea pig test methods and the local lymph node assay, no results indicative of sensitization were observed to methyl anthranilate (RIFM, 2007; Klecak, 1979, 1985). Additionally, no reactions indicative of skin sensitization were observed in the human maximization test and repeated insult patch test to either material (RIFM, 1973; RIFM, 1974; RIFM, 1964).

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/26/16.

10.1.9. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, and study data from the read-across analog ethyl anthranilate (CAS # 87-25-2), butyl anthranilate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for butyl anthranilate in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009). The structural analog, ethyl anthranilate (CAS # 87-

25-2; see Section 5) demonstrates an even greater degree of UV absorbance than the target material, and has sufficient study data to address phototoxicity and photoallergenicity; as such, it is a suitable read across analog. In *in vivo* phototoxicity and photoallergenicity studies with undiluted ethyl anthranilate, no phototoxic or photoallergic responses were reported (RIFM, 1976a; RIFM, 1976b). Based on UV/Vis absorption spectra and study data from the read-across analog ethyl anthranilate (CAS # 87-25-2), butyl anthranilate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/31/17.

10.1.11. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, butyl anthranilate, exposure level is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.12. Risk assessment

There are no inhalation data available on butyl anthranilate. Based on the Creme RIFM model, the inhalation exposure is 0.0015 mg/day. This exposure is 313 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.

Additional References: None.

Literature Search and Risk Assessment Completed on: 9/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of butyl anthranilate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, butyl 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 EPISUITE ver 4.1 did not identify butyl anthranilate as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

10.2.2. Risk assessment

Based on current volume of use (2011), butyl anthranilate does not present a risk to the aquatic compartment in the screening level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.3. Other available data

Butyl anthranilate has been pre-registered for REACH with no additional data at this time.

10.2.4. 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)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	7.985 mg/L			1,000,000	0.007985 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.74	3.74
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	Not reported	<1
Risk Characterization: PEC/PNEC	**N/A**	**N/A**

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

The RIFM PNEC is 0.007985 μg/L. The revised PEC/PNECs for EU (not reported) and NA: not applicable; cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 9/12/2016.

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/ntp_tox/index.cfm
- 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://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- EPA Actor: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- US EPA HPVIS: http://www.epa.gov/hpv/hpvis/index.html
- US EPA Robust Summary: http://cfpub.epa.gov/hpv-s/
- Japanese NITE: http://www.safe.nite.go.jp/english/db.html
- Japan Existing Chemical Data Base: http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- Google: https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.05.034.

Transparency document

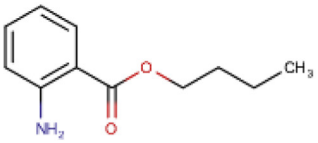
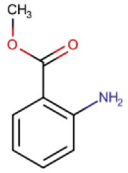
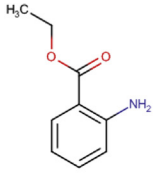
Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.05.034.

Appendix

Read across justification

Methods:

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- The Jmax values were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012)

	Target material	Read across material	
Principal Name	Butyl anthranilate	Methyl anthranilate	Ethyl anthranilate
CAS No.	7756-96-9	134-20-3	87-25-2
Structure			
Similarity (Tanimoto score)[1]		0.770	0.85
Read across endpoint		• Repeated dose • Developmental & Reproductive • Skin Sensitization • Genotoxicity	• Phototoxicity
Molecular Formula	$C_{11}H_{15}NO_2$	$C_8H_9NO_2$	$C_9H_{11}NO_2$

Molecular Weight	193.25	151.16	165.19
Melting Point (°C, EPISUITE)	86.18	55.76	66.17
Boiling Point (°C, EPISUITE)	309.84	263.57	279.90
Vapor Pressure (Pa @ 25°C, EPISUITE)	0.0399	2.63	1.37
Log Kow (KOWWIN v1.68 in EPISUITE)	3.74	1.88	2.57
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	30.4	2850	413.6
J_{max} (mg/cm^2/h, SAM)	26.987	50.57	120.19
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	2.87E-008	1.23E-008	1.23E-008

(***continued***).

Genotoxicity			
DNA binding (OASIS v 1.4 **QSAR Toolbox 3.4)**	• Radical mechanism via ROS formation • SN1, Nucleophilic attack	• Radical mechanism via ROS formation • SN1, Nucleophilic attack	
DNA binding by OECD **QSAR Toolbox (3.4)**	• SN1, Nitrenium Ion formation	• SN1, Nitrenium Ion formation	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Carcinogen (low reliability)	• Carcinogen (low reliability)	
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	• H-acceptor-path3-H-acceptor • Primary aromatic amine, hydroxyl amine and derived esters	• H-acceptor-path3-H-acceptor • Primary aromatic amine, hydroxyl amine and derived esters	

(***continued***).

Oncologic Classification	• Aromatic amine type compound	• Aromatic amine type compound	
Repeated dose toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Reproductive and developmental toxicity			
ER Binding by OECD QSAR Tool Box (3.4)	• Moderate binder NH_2 group	• Weak binder NH_2 group	
Developmental Toxicity Model by CAESAR v2.1.6	• Non toxicant (moderate reliability)	• Toxicant (low reliability)	
Skin Sensitization			
Protein binding by OASIS v1.1	• Acylation • AN2 • Michael type addition	• Acylation • AN2 • Michael type addition	
Protein binding by OECD	• No alert found	• No alert found	
Protein binding potency	• Not possible to classify	• Not possible to classify	
Protein binding alerts for skin	• No alert found	• No alert found	

(***continued***).

sensitization by OASIS v1.1			
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (low reliability)	• Non sensitizer (good reliability)	
Metabolism			
OECD QSAR Toolbox (v3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

(***continued***).

Summary:

There are insufficient toxicity data on butyl anthranilate (CAS # 7756-96-9). Hence *in-silico* evaluation was conducted by determining suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogs methyl anthranilate (CAS # 134-20-3) and ethyl anthranilate (CAS # 87-25-2) were identified as proper read across materials with data for their respective toxicity endpoints.

Conclusion/Rationale:

- Methyl anthranilate (CAS # 134-20-3) could be used as structurally similar read across analog for target material butyl anthranilate (CAS # 7756-96-9) for the genotoxicity, skin sensitization, reproductive and developmental toxicity, repeated dose toxicity endpoints.
  - The target substance and the read across analog are structurally similar and belong to the structural class of anthranilates.
  - The target substance and the read across analog have the methyl anthranilate fragment common among them.
  - The key difference between the target substance and the read across analog is that the target is an ester of butyl alcohol while the read across is an ester of methyl alcohol. This structure difference between the target substance and the read across analog do not raise additional structural alerts so the structure differences are not relevant from a toxicological perspective.
  - The target substance and the read across analog have Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the methyl anthranilate fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxicological perspective.
  - The physical chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - The target substance and the read across analogs has several genotoxicity alerts including carcinogen categorization by ISS model. The data described in the genotoxicity section above shows that the read across analog does not pose a concern for genetic toxicity. Therefore, the alerts are superseded by the availability of the data.
  - In spite of a structural alert due to presence of substituted amino group (Ashby and Tennant, 1988), presence of ortho carboxylic group might hinder the metabolic activation of the adjacent nitrogen substituent (Benigni and Bossa, 2006).
  - The target substance and read across analog is predicted to be a toxicant by CAESAR model for developmental toxicity. The data described in the developmental toxicity section above shows that the read across analog have adequate margin of exposure at the current level of use. Therefore, the alert is superseded by the availability of the data.
  - The target substance is predicted to be a sensitizer by CAESAR model for skin sensitization. The read-across substance is not predicted to be a sensitizer. The data described in the skin sensitization section above shows that the read across analog does not pose a concern for skin sensitization endpoint. Therefore, the alert is superseded by the availability of the data.
  - The target substance and the read across analog are expected to be metabolized similarly as shown by metabolism simulator.
  - The structural alerts for reproductive and developmental toxicity, repeated dose toxicity endpoints are consistent

between the metabolites of the read across analog and the target substance.
  - The structural differences between the target substance and the read across analog are deemed to be toxicologically insignificant.
- Ethyl anthranilate (CAS # 87-25-2) could be used as structurally similar read across analog for target material butyl anthranilate (CAS # 7756-96-9) for the phototoxicity endpoint.
  - The target substance and the read across analog are structurally similar and belong to the structural class of anthranilates.
  - The target substance and the read across analog have the methyl anthranilate fragment common among them.
  - The key difference between the target substance and the read across analog is that the target is an ester of butyl alcohol while the read across is an ester of ethyl alcohol. This structural difference between the target substance and the read across analog do not raise additional structural alerts so the structual differences are not relevant from a toxic endpoint perspective.
  - The target substance and the read across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the methyl anthranilate fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxicological perspective.
  - The physical chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - The target substance and the read across analog are expected to be metabolized similarly as shown by metabolism simulator.
  - The structural differences between the target substance and the read across analog are deemed to be toxicologically insignificant.

Explanation of Cramer Class: 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).

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,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 explanation) **No**
Q17.Readily hydrolysed 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**
Q32. Contains only the functional groups listed in Q30 or Q31 and either (a) a single fused non-aromatic carbocyclic ring or (b) aliphatic substituent chains longer than 5 carbon atoms or (c) a polyoxyethylene [(-OCH2CH2-)x, with x = 4] chain either on the aromatic ring or on an aliphatic side chain? **No** Q22. Common component of food? **Yes** Class Intermediate (Class II)

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