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Short review

RIFM fragrance ingredient safety assessment, methyl anthranilate, CAS Registry Number 134-20-3

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1. Identification

1 **Chemical Name:** Methyl anthranilate
2 **CAS Registry Number:** 134-20-3
3 **Synonyms:** o-Amino methyl benzoate; Benzoic acid, 2-amino-, methyl ester; Methyl 2-aminobenzoate; Methyl *o*-aminobenzoate; Methyl anthranilate; 2-Aminobenzoic acid, methyl ester; アミノ安息香酸アルキル(C = 1 ~ 10)
4 **Molecular Formula:** $C_8H_9NO_2$
5 **Molecular Weight:** 151.16
6 **RIFM Number:** 173

2. Physical data

1. **Boiling Point:** 255 °C [FMA database], (calculated) 263.57 °C [EPI Suite]
2. **Flash Point:** >212 °F; CC [FMA database]
3. **Log K_{OW}:** 1.9 at 25 °C [RIFM, 1995], 2.26 [EPI Suite]
4. **Melting Point**: 55.76 °C [EPI Suite]
5. **Water Solubility:** 1860 mg/L [EPI Suite]

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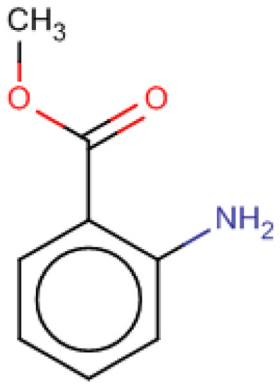
Version: 041817. This version replaces any previous versions.
Name: Methyl anthranilate
CAS Registry Number: 134-20-3



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 show that this material is not genotoxic, provided a MOE >100 for the repeated dose and developmental toxicity endpoints, and it does not have skin sensitization potential. 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 suitable 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; its risk quotients, based on current volume of use in Europe and North America, were acceptable (PEC/PNEC <1).

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(Mortelmans et al., 1986; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day	(Hagan et al., 1967)
Developmental and Reproductive Toxicity: Developmental NOAEL = 768.4 mg/kg/day. No reproductive NOAEL. Exposure is below the TTC.	(RIFM, 2012)
Skin Sensitization: Not sensitizing	(RIFM, 2007; RIFM, 1973a; RIFM, 1974a; RIFM, 1964)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	

(*continued on next page*)

(*continued*)

	(UV Spectra, RIFM DB; RIFM, 1976a; RIFM, 1976b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 97% (OECD 301B)	(RIFM, 1994)
Bioaccumulation: Screening Level: 8.08 L/kg	(EpiSuite ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: Algae EC50: 11.67 mg/L	(EpiSuite ver 4.1)
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: Algae EC50: 11.67 mg/L	(EpiSuite ver 4.1)
RIFM PNEC is: 1.167 μg/L	
•Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1	

6. **Specific Gravity:** 1.17 g/ml [RIFM, 1994], 1.163–1.171 [FMA database], 1.161–1.169 [FMA database]
7. **Vapor Pressure:** 0.0124 mm Hg @ 20 °C [EPI Suite 4.0], 0.01 mm Hg 20 °C [FMA database], 0.0197 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark ($1000\ L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless to pale yellow liquid or crystals with bluish fluorescence and grape-like or orange odor musty fruity somewhat dry floral odor reminiscent of concord grapes, orange blossom and having a good tenacity. The odor appears much sweeter at high dilution. Sweet fruity grape like taste with a distinct floral perfumed character.

3. Exposure

1. Volume of Use (worldwide band): 100–1000 metric tons per year (IFRA , 2011)
2. 95th Percentile Concentration in Hydroalcoholics: 0.14% (RIFM, 2014)
3. Inhalation Exposure*: 0.00039 mg/kg/day or 0.028 mg/day (RIFM, 2014)
4. Total Systemic Exposure:** 0.0013 mg/kg/day (RIFM, 2014)

*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:** 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*	II	III

*See Appendix below for explanation.

2 **Analogues Selected:**
- a **Genotoxicity:** None
- b **Repeated Dose Toxicity:** None
- c **Developmental and Reproductive Toxicity:** None
- d **Skin Sensitization:** None
- 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)

Methyl anthranilate is reported to occur in nature in the following*:

Babaco fruit (*Carica pentagona Heilborn*) Citrus fruits Cocoa Grape (Vitis species) Honey Rice (*Oryza sativa* L.) Starfruit (*Averrhoa carambola* L.) Strawberry (Fragaria species) Tea Wine.

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1–Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, 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

1Human Health Endpoint Summaries:

10.1. Genotoxicity

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

10.2. Risk assessment

The mutagenic potential of methyl anthranilate was assessed in an Ames study conducted by the National Toxicology Program and in accordance with OECD TG 471 using the modified preincubation method. *S. typhimurium* strains TA1535, TA98, TA100 and TA1537 were treated with methyl anthranilate in DMSO (dimethyl sulfoxide) at concentrations between 33 and 1800 μg/plate both with and without metabolic activation (Mortelmans et al., 1986). The test material did not induce an increase in the amount of revertant colonies in any of the test strains and was considered to be not mutagenic under the conditions of the study.

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 at concentrations up to 1512 μg/mL in the presence and absence of metabolic activation (S9) at the 3 h and 24-hour 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.

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

Additional References: Kasamaki et al., 1982; Fujita and Sasaki, 1987; Oda et al., 1978; Yoo, 1986; Kawachi et al., 1981; Foltinova and Grones, 1997; Miyagawa et al., 1995; Hughes et al., 2012; Fowler et al., 2012.

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

10.3. Repeated dose toxicity

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

10.4. Risk assessment

There are sufficient repeated dose toxicity data on methyl anthranilate. 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 methyl 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 methyl anthranilate, 500/0.0013 or 384615.

In addition, the total systemic exposure to methyl anthranilate (1.3 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: Stoner et al., 1973; Schafer and Bowles, 1985; Clark et al., 1980; Cutting et al., 1966; Verrett et al., 1980; RIFM, 1974b; Grundschober, 1977; RIFM, 1978; Ekman and Strombeck, 1949; Oser et al., 1965; Clark et al., 1980; RIFM, 1963; Yamaori et al., 2005; Dahl and Hadley, 1983.

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

10.5. Developmental and reproductive toxicity

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

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

10.6. Risk assessment

The developmental toxicity data on methyl anthranilate are sufficient for the developmental toxicity endpoint. 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 fetuses 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 methyl 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 methyl anthranilate, 768.4/0.0013 or 591077.

In addition, the total systemic exposure to methyl anthranilate (1.3 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 reproductive toxicity data on methyl anthranilate or any of the read across materials. The total systemic exposure for methyl anthranilate (1.3 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: Stoner et al., 1973; Schafer and Bowles, 1985; Clark et al., 1980; Cutting et al., 1966; Verrett et al., 1980; RIFM, 1974b; Grundschober, 1977; Yamaori et al., 2005; RIFM, 1978; Ekman and Strombeck, 1949; Oser et al., 1965; Clark et al., 1980; RIFM, 1963; Yamaori et al., 2005; Dahl and Hadley, 1983.

Literature Search and Risk Assessment Completed on: 9/14/2016.

10.7. Skin sensitization

Based on the existing data, methyl anthranilate does not present a concern for skin sensitization.

10.8. Risk assessment

Based on the available data, methyl anthranilate does not present a concern for skin sensitization. The chemical structure of this material indicates that it 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 (RIFM, 2007; Klecak, 1979, 1985). Additionally, no reactions indicative of skin sensitization were observed in the human maximization test or repeated insult patch test (RIFM, 1973a; RIFM, 1974a; RIFM, 1964).

Additional References: None.

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

10.9. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra and study data from the read across material, ethyl anthranilate (CAS # 87-25-2), methyl anthranilate does not present a concern for phototoxicity or photoallergenicity.

10.10. Risk assessment

The available UV/Vis spectra (OECD test guideline 101) for methyl anthranilate indicate minor absorbance between 290 and 700 nm. Molar absorption coefficient for wavelengths between 290 and 700 nm is below the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$) considered to be of concern for phototoxic effects (Henry et al., 2009). A phototoxicity study in hairless mice was conducted and weakly positive responses (no further details provided) were reported with 12.5% and 100% methyl anthranilate (RIFM, 1979). As a non-UV treated control group was not present, it is not possible to conclude on whether the responses were phototoxicity or irritation. The structural analogue, ethyl anthranilate (CAS # 87-25-2) 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 analogue. 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 analogue ethyl anthranilate (CAS # 87-25-2), methyl anthranilate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

10.11. Local respiratory toxicity

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

10.12. Risk assessment

There are limited inhalation data available on methyl anthranilate. Based on the Creme RIFM model, the inhalation exposure is 0.028 mg/day. This exposure is 16.8 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: RIFM, 1973b; Buchbauer et al., 1993; Marples and Roper, 1997; Johnson et al., 2005.

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

2 Environmental Endpoint Summary:

10.13. Screening-level assessment

A screening level risk assessment of methyl anthranilate was performed following the RIFM Environmental Framework (Salvito et al., 2002) that 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 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, methyl anthranilate was identified as a fragrance material with 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 methyl anthranilate as persistent or bioaccumulative based on its structure and physical-chemical properties. A screening-level hazard assessment using EPISUITE ver 4.1 did not identify methyl dihydrojasmonate as either being possibly persistent nor bio-accumulative 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). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.14. Risk assessment

Based on current volume of use (2011), methyl anthranilate presents a risk to the aquatic compartment in the screening level assessment.

10.15. Key studies

10.15.1. Biodegradation

RIFM, 1996: The ready biodegradability of methyl anthranilate was determined by the Manometric Respirometry Test according to OECD 301F guidelines. 100 mg/L of the test material underwent 85% biodegradation after 28 days in the test conditions.

RIFM, 1994: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test according to the OECD 301B method. Methyl anthranilate biodegraded 97% in 28 days.

10.15.2. Ecotoxicity

Clark et al., 1993: The 96-hour LC50 values of methyl anthranilate in catfish fry, rainbow trout fry, Atlantic salmon fry and bluegill fry were 16.23, 22.91, 32.35 and 9.12 mg/L, respectively.

10.15.3. Other available data

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

10.16. Risk assessment refinement

Since Methyl anthranilate has passed the screening level, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	249.1 mg/L			1,000,000	0.2491 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** Ver 1.11	14.15 mg/l	28.6 mg/l	11.67 mg/l	10,000	1.167 μg/l	Esters
ECOSAR Acute Endpoints **(Tier 2)** Ver 1.11	40.97 mg/l	11.72 mg/l	39.01 mg/l			Anilines (hindered)
ECOSAR Acute Endpoints **(Tier 2)** Ver 1.11	71.82 mg	41.78 mg/l	34.44 mg/l			Neutral Organics (SAR)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.9	1.9
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
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 1.167 μg/L. The revised PEC/PNECs for EU and NA <1 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: 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/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

1. Read across justification

1.1. Methods

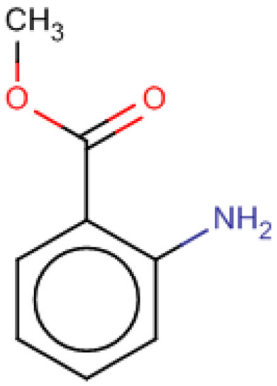
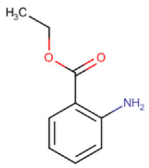
- The identified read across analogs were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of the target substance and the read across analog were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- Jmax 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 generated 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.2.1.7 and 2.1.6, respectively (Cassano et al., 2010).
- Protein binding was 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).

1.2. Summary

There are insufficient toxicity data on methyl anthranilate (CAS # 134-20-3). 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 analog ethyl anthranilate (CAS # 87-25-2) was identified as a proper read across material with data for its respective toxicity endpoints.

1.3. Conclusion/Rationale

- Ethyl anthranilate (CAS # 87-25-2) could be used as structurally similar read across analog for target material methyl anthranilate (CAS # 134-20-3) 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 anthranilate fragment common among them.
- The key difference between the target substance and the read across analog is that the target has a methyl group on the alcohol portion of the ester while the read across has an ethyl group at the same position. This structural difference between the target substance and the read across analog do not raise additional structural alerts so the structural differences are not relevant from a toxicological 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

	Target material	Read across material
Principal Name	Methyl anthranilate	Ethyl anthranilate
CAS No.	134-20-3	87-25-2
Structure		
Similarity (Tanimoto score)[1]		0.892
Read across endpoint		• Phototoxicity
Molecular Formula	$C_8H_9NO_2$	$C_9H_{11}NO_2$
Molecular Weight	151.16	165.19
Melting Point (°C, EPISUITE)	55.76	66.17
Boiling Point (°C, EPISUITE)	263.57	279.90
Vapor Pressure (Pa @ 25 °C, EPISUITE)	2.63	1.37
Log Kow (KOWWIN v1.68 in EPISUITE)	1.88	2.57
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	2850	413.6
J_{max} (mg/cm^2/h, SAM)	50.57	120.19
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.23E-008	1.23E-008
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

differences in the structure which are responsible for Tanimoto score <1 are not relevant 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)

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.06.003.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.06.003.

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