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Short review

RIFM fragrance ingredient safety assessment, methyl *N*-acetylanthranilate, CAS Registry Number 2719-08-6

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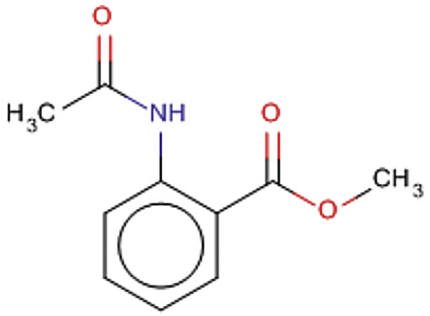


Abbreviation list:
2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data 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 was reviewed for 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, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the target material and the read across analog benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (CAS # 25628-84-6) show that this material is not genotoxic. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.0015 mg/kg/day and 0.47 mg/day, respectively). Data on the target material show that this material does not have skin sensitization potential. The repeated dose toxicity endpoint was completed using acetic acid (CAS# 64-19-7), methyl anthranilate (CAS# 134-20-3) and benzoic acid, 2-amino- (CAS# 118-92-3) as read across analogs, which provided a MOE > 100. The developmental toxicity endpoint was completed by using acetic acid (CAS# 64-19-7) and methyl anthranilate (CAS# 134-20-3) as read across analogs, which provided a MOE > 100. Data on the target material show that this material is not phototoxic. The photoallergenicity endpoint was completed based on data from the read across analog methyl *N*-methyl anthranilate (CAS# 85-91-6). The environmental endpoints were evaluated and methyl n-acetylanthranilate (CAS# 2719-08-6) 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	(RIFM, 2014; RIFM, 2013b)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day	(Hagan, 1967)
Developmental Toxicity: NOAEL = 768.4 mg/kg/day and **Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.	(RIFM, 2012)
Skin Sensitization: Not sensitizing	(RIFM, 1993a; RIFM, 1993b; RIFM, 1982; RIFM, 1966)
Phototoxicity/Photoallergenicity: Not phototoxic/Not photoallergenic	(RIFM, 2015; RIFM, 1978a)

(*continued on next page*)

(*continued*)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Screening Level: 2.85 (Biowin 3) (EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 5.69 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level Fish LC50: 447.6 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: LC50: 447.6 mg/l (Salvito et al., 2002)
RIFM PNEC is: 0.4476 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe Not Applicable: Cleared at Screening Level

1. Identification

1. **Chemical Name:** Methyl *N*-acetylanthranilate
2. **CAS Registry Number:** 2719-08-6
3. **Synonyms:** o-Acetamidobenzoic acid methyl ester; benzoic acid, 2-(acetylamino)-, methyl ester; methyl *N*-acetylanthranilate; methyl 2-acetamidobenzoate; methyl 2-(acetylamino)benzoate; n-acetyl methyl anthranilate; benzoic acid, 2-(acetylamino)-, methyl ester; anthranilic acid, *N*-acetyl-, methyl ester; methyl 2-(acetylamino)benzoate; methyl *N*-acetoanthranilate; o-(methoxycarbonyl)acetanilide
4. **Molecular Formula:** $C_{10}H_{11}NO_3$
5. **Molecular Weight:** 193.2
6. **RIFM Number:** 1301

2. Physical data

1. **Boiling Point:** 370 °C [RIFM database], 355.32 °C [EPI Suite]
2. **Flash Point:** 212°F [RIFM database]
3. **Log K_{OW}:** 1.73 [EPI Suite]
4. **Melting Point**: 97.0 [RIFM database], 101 °C [RIFM database], (calculated) 126.43 °C [EPI Suite]
5. **Water Solubility:** 1847 mg/L [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00000463 mm Hg @ 20 °C [EPI Suite 4.0], 0.001 mm Hg @20C [FMA database], 9.6e-006 mm Hg @ 25 °C [EPI Suite]
8. **UV spectra:** Absorbance between 290 and 700 nm, with peak at 300 nm and returning to baseline by 350 nm; molar absorption coefficient above the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** White to light yellow crystals with a low/very mild fruity, powdery, and strawberry odor.*

*http://www.thegoodscentscompany.com/data/rw1015551.html, retrieved 1/22/14.

3. Exposure

1. **Volume of Use (worldwide band):** <1 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0045% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000022 mg/kg/day or 0.0017 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00059 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 III, High (Expert Judgment)

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

*See Appendix below for explanation Cramer.

2. Analogues Selected:
   a. **Genotoxicity:** Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (CAS # 25628-84-6)
   b. **Repeated Dose Toxicity:** Acetic acid (CAS# 64-19-7), methyl anthranilate (CAS# 134-20-3) and benzoic acid, 2-amino- (CAS# 118-92-3)
   c. **Developmental and Reproductive Toxicity:** Acetic acid (CAS# 64-19-7) and methyl anthranilate (CAS# 134-20-3)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None (phototoxicity)/ methyl *N*-methylanthranilate (CAS# 85-91-6; photoallergenicity)
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification: See Appendix below**

6. Metabolism

Metabolism was considered for some endpoint evaluations.

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

Methyl *N*-acetylanthranilate is reported to occur in the following foods*:

Honey

*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 data, methyl *N*-acetylanthranilate does not present a concern for genetic toxicity.

10.1.2. Risk assessment

Methyl *N*-acetyl anthranilate was assessed in the BlueScreen assay and found not genotoxic with metabolic activation and genotoxic without metabolic activation; however, considering that genotoxicity occurred in the presence of cytotoxicity (RIFM, 2013a). There are no data assessing the mutagenic activity of methyl *N*-acetylanthranilate however, read across can be made to benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (CAS # 25628-84-6; see Section 5). The mutagenic activity of benzoic acid, 2-[(1-oxopropyl) amino]-, methyl ester (CAS # 25628-84-6) 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 TA1535, TA1537, TA98, TA100 and *Escherichia coli* strains WP2uvrA were treated with benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2014). Under the conditions of the study, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester was not mutagenic in the Ames test.

The clastogenic activity of methyl *N*-acetylanthranilate 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 *N*-acetylanthranilate in DMSO (dimethyl sulfoxide) at concentrations up to 1932 μg/mL in the presence and absence of metabolic activation (S9) at the 4 h and 24 h time points. Methyl *N*-acetylanthranilate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2013b). Under the conditions of the study, methyl *N*-acetylanthranilate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on all the information, methyl *N*-acetyl anthranilate does not present a concern for genotoxic potential.

Additional References: RIFM, 1987.

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

10.1.3. Repeated dose toxicity

The margin of exposure for methyl *N*-acetylanthranilate 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 methyl *N*-acetylanthranilate. Methyl *N*-acetylanthranilate is expected to hydrolyze to acetic acid (CAS# 64-19-7; see Section 5), methyl anthranilate (CAS# 134-20-3; see Section 5) and benzoic acid, 2-amino- (also called anthranilic acid; CAS# 118-92-3; see Section 5). The metabolite, acetic acid, has been reviewed by several agencies. The US-Food and Drug Administration (FDA, 21CFR184.1005, revised as of April 1, 2016; accessed on 12/18/2016) has granted acetic acid a generally recognized as safe (GRAS) status. JECFA, 2006 (accessed on 12/18/2016) also evaluated acetic acid and states that for acetic acid it is not necessary to indicate acceptable daily intakes for man. The European food safety authority (EFSA), reviewed the data on acetic acid (Scientific Opinion on the safety and efficacy of acetic acid, sodium diacetate and calcium acetate as preservatives for feed for all animal species, 2012; accessed on 12/18/2016). They state that there is now an application for the reauthorization of acetic acid and these salts as preservatives in feed and for a new use of acetic acid as a preservative in water for drinking. They may be used alone or in combination with other organic acids typically in a concentration 200 to 2500 mg acetate/kg complete feeding stuffs. The Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) provides a comprehensive review of the toxicity data on acetic acid as a part of their Human health Tier II assessment for Acetic acid; accessed 12/18/2016. They state that acetates are normal components in human and animal diets. They are produced in small (molar) quantities daily in the gastrointestinal tract, where they are rapidly and completely metabolized. Acetate is produced as a major intermediate in normal metabolic processes. Various isotope experiments have shown that the different carbon atoms of acetic acid are used in glycogen formation as intermediates of carbohydrates and fatty acid synthesis, as well as in cholesterol synthesis. In addition, acetic acid also participates in the acetylation of amines and formation of proteins of plasma, liver, kidney, gut mucosa, muscle and brain. Acetic acid is absorbed from the gastrointestinal tract and through the lungs. Following absorption, acetic acid is almost completely metabolized by most tissues and may give rise to the production of ketone bodies as intermediates. The level of the acetate ion in humans has been estimated at about 50–60 μmol/L (3.0–3.6 mg/L) in plasma and 116 μmol/L (7 mg/L) in cerebrospinal fluid. Daily turnover of the acetate ion in humans is estimated at about 7.5 μmol/kg/min representing about 45 g/day. Based on the treatment-related effects reported in limited repeated dose toxicity studies, acetic acid is not considered to cause serious damage to health from repeated oral exposure. The effects observed in some cases could have been only due to the corrosive activity of acetic acid. Results from repeated oral, inhalation, and dermal exposure of humans to acetic acid has been reported with effects on the gastrointestinal tract, digestive disorders including heartburn and constipation, chronic inflammation of the respiratory tract, pharyngitis, catarrhal bronchitis, darkening of skin, skin dermatitis, and erosion of the exposed front teeth enamel. In addition, skin on the palms of hands can become dry, cracked and hyperkeratotic. These observed effects were not associated with any systemic findings, suggesting the effects observed could be due to its corrosive activity. Based on the limited data available, acetic acid is not likely to be a carcinogen. Based on the available data, acetic acid does not show specific reproductive or developmental toxicity. Thus, acetic acid does not pose repeated dose, developmental or reproductive toxicity to human health when used in fragrances.

Metabolite methyl anthranilate was administered via diet to 10 weanling Osborne-Mendel rats/per sex/group for 90 days at doses of 0, 1000, and 10000 ppm, equivalent to 0, 50, and 500 mg/kg/day (as per the conversion factors for old-rats available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives). There were no effects on growth or hematology and no macroscopic or microscopic histopathological lesions. The NOAEL for

methyl anthranilate was determined to be 10000 ppm, equivalent to 500 mg/kg/day (Hagan et al., 1967; Bar and Griepentrog, 1967). In another study, Fischer 344 rats or B6C3F1 mice when treated with metabolite anthranilic acid administered via diet at doses up to 30,000 ppm and 50,000 ppm, to rats and mice respectively, for 2 years showed no treatment-related evidence of carcinogenicity (RIFM, 1978b). The dietary dose in rats and mice 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 most conservative NOAEL for the repeated dose toxicity endpoint was determined to be 500 mg/kg/day for methyl anthranilate from the studies conducted on rats (Hagan et al., 1967). Therefore, the methyl *N*-acetylanthranilate 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 *N*-acetylanthranilate, 500/0.00059 or 847458.

In addition, the total systemic exposure to methyl *N*-acetylanthranilate (0.59 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) for the repeated dose toxicity endpoint for a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 12/19/2016.

10.1.5. Developmental and reproductive toxicity

The margin of exposure for methyl *N*-acetylanthranilate is adequate for the developmental toxicity endpoint at the current level of use. There are insufficient reproductive toxicity data on methyl *N*-acetylanthranilate or any read across materials. The total systemic exposure to methyl *N*-acetylanthranilate is below the TTC for the reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

10.1.6. Risk assessment

There are no developmental or reproductive toxicity data on methyl *N*-acetylanthranilate. Methyl *N*-acetylanthranilate is expected to hydrolyze to acetic acid (CAS# 64-19-7; see Section 5), methyl anthranilate (CAS# 134-20-3; see Section 5) and benzoic acid, 2-amino- (also called anthranilic acid; CAS# 118-92-3; see Section 5). Metabolite, acetic acid, has been reviewed by several agencies, as stated above, in the repeated dose toxicity section of this safety assessment. Acetic acid does not pose repeated dose, developmental, or reproductive toxicity concerns to human health when used in fragrances. Metabolite, methyl anthranilate, has sufficient developmental toxicity data. Methyl anthranilate was administered via diet to a group of 25 presumed pregnant Crl:CD(SD) female rats/dose group. The rats were fed methyl anthranilate in the diet at dose levels of 0, 1000, 5000 and 10000 ppm (average daily consumption of 0, 80.4, 389.9 and 768.4 mg/kg/day) on Days 6 through 20 of presumed gestation. Exposure to methyl anthranilate in the diet at 1000, 5000 and 10000 ppm resulted in reduced body weight gains and food consumption at 5000 and 10000 ppm but did not produce any developmental toxicity at exposure levels as high as 10000 ppm. Even in the presence of slight maternal toxicity (reduced body weight gains), no effects were observed on any of the investigated developmental parameters of the fetus. Based on the results of this study, the NOAEL for developmental toxicity was greater than 10000 ppm, equivalent to 768.4 mg/kg/day (RIFM, 2012). There are no developmental toxicity data on metabolite anthranilic acid. Thus, the most conservative NOAEL of 768.4 mg/kg/day was considered for the developmental toxicity endpoint. Therefore, the methyl *N*-acetylanthranilate 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 *N*-acetylanthranilate, 768.4/0.00059 or 1302373.

There are no reproductive toxicity data on methyl *N*-acetylanthranilate, methyl anthranilate (CAS# 134-20-3; see Section 5) and anthranilic acid (CAS# 118-92-3; see Section 5). Acetic acid does not pose repeated dose, developmental or reproductive toxicity to human health when used in fragrances. Thus, a NOAEL for methyl *N*-acetylanthranilate could not be derived for the reproductive toxicity endpoint.

The total systemic exposure to methyl *N*-acetylanthranilate (0.59 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) for the developmental and reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 12/19/2016.

10.1.7. Skin sensitization

Based on the existing data, methyl *N*-acetylanthranilate does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the available data, methyl *N*-acetylanthranilate does not present a concern for skin sensitization. The chemical structure of this material indicates that it could potentially be protein reactive (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). However, in guinea pig test methods no results indicative of sensitization were observed (RIFM, 1993a; RIFM, 1982). Additionally, no reactions indicative of skin sensitization were observed in human repeated insult patch tests (RIFM, 1993b; RIFM, 1966).

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/23/16.

10.1.9. Phototoxicity/Photoallergenicity

Based on *in vitro* study data, methyl *N*-acetylanthranilate does not present a concern for phototoxicity. Based on human data on read across analog methyl *N*-methylanthranilate (CAS # 85-91-6), methyl *N*-acetylanthranilate does not present a risk for photoallergenicity.

10.1.10. Risk assessment

The available UV/Vis spectra (OECD test guideline 101) for methyl *N*-acetylanthranilate demonstrate that this material absorbs in the region of 290–700 nm, with peak absorbance at 300 nm and returning to baseline by 350 nm. The molar absorption coefficient for maximum absorbance between 290 and 700 nm is above the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$) of concern for phototoxic effects (Henry et al., 2009). In an *in vitro* 3T3 Neutral Red uptake assay, methyl *N*-acetylanthranilate was not predicted to be phototoxic based on mean photo-effect (RIFM, 2015). Based on the *in vitro* study data, methyl *N*-acetylanthranilate does not present a concern for phototoxicity.

Based on the available UV/Vis spectra, methyl *N*-acetylanthranilate has the potential for photoactivation. Suitable photoallergenicity study data are not available for methyl *N*-acetylanthranilate. The structural analog, methyl *N*-methylanthranilate demonstrates an even greater degree of UV absorbance than the target material, and has sufficient study data to address photoallergenicity; as such, it is a suitable read across analog for the photoallergenicity endpoint. In a photoallergenicity study conducted in human volunteers, no photoallergic responses were reported with 5% methyl *N*-methylanthranilate (RIFM, 1978a). Based on human data on read across analog methyl *N*-methylanthranilate, methyl *N*-acetylanthranilate does not present a risk for 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, methyl *N*-acetylanthranilate, 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 methyl *N*-acetylanthranilate. Based on the Creme RIFM model, the inhalation exposure is 0.0017 mg/day. This exposure is 276 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 methyl *N*-acetylanthranilate 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 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 *N*-acetylanthranilate 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 identify methyl *N*-acetylanthranilate as not persistent and not bioaccumulative based on its structure and physical-chemical properties. his screening evel 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), methyl *N*-acetylanthranilate does not present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.4. Other available data

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

10.2.5. 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)**	447.6 mg/L			1,000,000	0.4476 μg/l	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.73	1.73
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.4476 μg/L. The revised PEC/PNECs for EU and NA: Not applicable: Cleared at screening level at current 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.

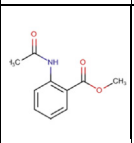
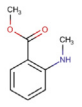
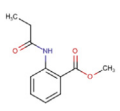
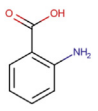
This is not an exhaustive list.

Appendix

Read across justification

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™ version 4.11 (USEPA, 2012).
- Jmax was calculated using RIFM skin absorption model (SAM) and the 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 version 3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (version 3.4) (OECD, 2012).

	Target material	Read across material				
Principal Name	Methyl N-acetylanthranilate	Methyl anthranilate	Methyl N-methylanthranilate	Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester	Acetic acid	Benzoic acid, 2-amino-
CAS No.	2719-08-6	134-20-3	85-91-6	25628-84-6	64-19-7	118-92-3
Structure						
Similarity (Tanimoto score)[1]		NA	0.887	0.933	NA	NA
Read across endpoint		• Repeated dose • Developmental & Reproductive	• Phototoxicity	• Genotoxicity	• Repeated dose • Developmental and Reproductive	• Repeated dose
Molecular Formula	$C_{10}H_{11}NO_3$	$C_8H_9N\ O_2$	$C_9H_{11}NO_2$	$C_{11}H_{13}NO_3$	$C_2H_4O_2$	$C_7H_7NO_2$
Molecular Weight	193.2	151.16	165.19	207.23	60.05	139.15
Melting Point (°C, EPISUITE)	126.43	55.76	42.10	134.33	-21.26	94.08
Boiling Point (°C, EPISUITE)	355.32	263.57	249.86	366.92	122.30	307.7

	Target material	Read across material				
Vapor Pressure (Pa @ 25°C, EPISUITE)	0.00128	2.63	2.78	0.000555	2.29e+003	0.0105
Log Kow (KOWWIN v1.68 in EPISUITE)	1.65	1.88	2.81	2.22	-0.17[1]	1.21
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	1847	2850	257	514.3	475900	3500
J_{max} (mg/cm²/h, SAM)	34.28	50.57	74.151	14.671	6283.004	29.603
Henry's Law (Pa·m³/mol, Bond	3.98E-011	1.23E-008	2.69E-008	5.28E-011	5.48E-007	3.83E-011
Method, EPISUITE)						
Genotoxicity						
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found			• No alert found		

	Target material	Read across material				
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found			• No alert found		
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Carcinogen (moderate reliability)			• Non carcinogen (moderate 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	• Aromatic N-acyl amine			• No alert found •		
In-vivo mutagenicity (Micronucleus) alerts by ISS	• Aromatic N-acyl amine • H-acceptor-path3-H-acceptor			• H-acceptor-path3-H-acceptor		
Oncologic Classification	• Not classified			• Not classified		
Repeated dose toxicity						
Repeated Dose (HESS)	• Not categorized	• Not categorized			• Carboxylic acid (Hepatotoxicity)	• Not categorized

	Target material	Read across material				
Reproductive and developmental toxicity						
ER Binding by OECD QSAR Tool Box (3.4)	• Non binder without OH and NH_2 group	• Weak binder NH_2 group			• Non binder, non cyclic structure	
Developmental Toxicity Model by CAESAR v2.1.6	• Non toxicant (good reliability)	• Toxicant (low reliability)			• toxicant (low reliability)	
Metabolism						
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	• NA	See Supplemental data 2	See Supplemental Data 3	• NA	• NA

1. (Patel et al., 2002).

NA: Not applicable, either direct metabolite or the analog of a direct metabolite of the target.

Summary

There are insufficient toxicity data on methyl *N*-acetylanthranilate (CAS # 2719-08-6). 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), methyl *N*-methylanthranilate (CAS # 85-91-6) and benzoic acid, 2-[(1-oxopropyl) amino]-, methyl ester (CAS # 25628-84-6) were identified as proper read across materials with data for their respective toxicity endpoints.

- Metabolism

Metabolism of target material methyl *N*-acetylanthranilate (CAS # 2719-08-6) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). The target material is metabolized to methyl anthranilate (CAS # 134-20-3) and methyl alcohol (CAS 67-56-1) in the first step with 0.35 intrinsic probability. Methyl *N*-methylanthranilate (CAS # 85-91-6) is structurally similar to major metabolite methyl anthranilate of the target, thus methyl *N*-methylanthranilate could be used as the read across material for the target material. Methyl *N*-methylanthranilate was out of domain for *in vivo* and *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgement, the model's domain exclusion was overridden and a justification is provided.

Conclusion/Rationale

- Methyl anthranilate (CAS # 134-20-3), methyl *N*-methylanthranilate (CAS # 85-91-6), acetic acid (CAS # 64-19-7) and benzoic acid, 2-amino- (CAS # 118-92-3) were used as a structurally similar read across analog for methyl *N*-acetylanthranilate (CAS # 2719-08-6) for the phototoxicity, repeated dose, developmental and reproductive toxicity endpoints.
  - o The read across materials are major metabolites or are analogs of the major metabolites of the target.
  - o The target is an anthranilate which metabolizes to methyl anthranilate. Methyl *N*-methylanthranilate is a structurally similar analog of methyl anthranilate.

- The structural differences in the target and the read across analogs can be mitigated by the fact that the target could be metabolically hydrolyzed to read across analogs used here. Therefore, the toxicity profile of the target is expected to be similar to that of the metabolites.
- The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by an amino benzoate fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevant from a toxicity perspective.
- The target substance and the read across analogue have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant.
- According to the QSAR OECD Toolbox version 3.4, structural alerts for the skin sensitization endpoint are consistent between the target substance and the read across analogue.
- The target substance and the read across analogue are expected to metabolize differently. Since the read across analogue is a secondary amine, it will be a substrate for MAO (monoamine oxidase), yielding a primary amine formaldehyde.
- The read across analog acetic acid for repeated dose toxicity are categorized as carboxylic acid substances with hepatotoxicity alert while the target substance is not categorized by HESS categorization scheme. It has been shown by numerous literature that carboxylic acids are excreted out from human body relatively quickly with no toxic effects. The data described in repeated dose section above shows that the margin of exposure of the read across analog is adequate at the current level of use. Therefore, the alert will be superseded by the availability of data.
- The read across analog methyl anthranilate is shown to have ER binding alert while no such alert is given for the target substance. ER Binding is a molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
- According to the CAESAR model for developmental toxicity, the read across analog methyl anthranilate is predicted to be a toxicant while the target substance is not predicted to be a toxicant. The data described in the developmental toxicity section shows that the read across analog has adequate margin of exposure at the current level of use. Therefore, the alert will be superseded by the availability of the data.
- The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

- Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (CAS # 25628-84-6) could be used as a structurally similar read across analog for target material methyl *N*-acetylanthranilate (CAS # 2719-08-6) for the genotoxicity endpoint.
  - The target substance and the read across analogue are structurally similar and belong to the structural class of 2-aceta aminobenzoates.
  - The target substance and the read across analogue have the 2-aceta aminobenzoate fragment common among them.
  - The key difference between the target substance and the read across analogue is that they have different alkyl groups on the *N*-acyl site. The target substance has a methyl group while the read across has an ethyl group. This structural difference between the target substance and the read across analogue does not raise additional structural alerts and are not relevant from a toxicological perspective.
  - The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the anthranilate (ester form) fragment. The 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.
  - According to ISS model for carcinogenicity, the target material is predicted to be carcinogenic with low reliability while the read across analog is predicted to be non-carcinogenic. The data described in the genotoxicity section above show that the read across analog does not pose a concern for genetic toxicity. Based on the structural similarity between the target substance and the read across analog and data availability for read across analog, this alert will be superseded by availability of data.
  - The target substance and the read across analogue are expected to be metabolized similarly as shown by metabolism simulator.
  - The structural differences between the target substance and the read across analogue 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, 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
19. 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 'Residue 1'
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 (n >= 4) on the aromatic or aliphatic side chain? No 'Residue 1'
Q22. Common component of food? No 'Residue 1'
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 'Residue 1' Class High (Class III)

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.05.030.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.05.030.

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