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RIFM fragrance ingredient safety assessment, methyl N-methylanthranilate, CAS Registry Number 85-91-6

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RIFM Fragrance Ingredient Safety Assessments is here: **fragrancematerialsafetyresource.elsevier.com**.
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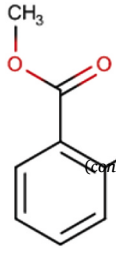
CAS Registry Number: 85-91-6



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
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., 2015a, 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

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Methyl N-methylanthranilate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl N-methylanthranilate is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on analog methyl anthranilate (CAS # 134-20-3) provide a calculated MOE >100 for the developmental toxicity endpoint. The fertility and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material; exposure is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). Data show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data; methyl N-methylanthranilate is phototoxic with a limit of 0.1% but not photoallergenic. The environmental endpoints were evaluated; methyl N-methylanthranilate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2003; RIFM, 2015b)
Repeated Dose Toxicity: NOAEL = 244 mg/kg/day.	Gaunt (1970)
Reproductive Toxicity: Developmental NOAEL = 768.4 mg/kg/day. No fertility NOAEL. Exposure is below the TTC.	RIFM (2012)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(Klecak, 1977; Klecak, 1985; RIFM, 1974a)
Phototoxicity/Photoallergenicity: Phototoxic. NOEL for phototoxicity = 0.5%; Maximum Acceptable Concentration = 0.1%. Not photoallergenic.	(RIFM, 2010a; RIFM, 2010b; RIFM, 2010c; RIFM, 2002; Kaidbey, 1980; RIFM, 1978b; RIFM, 1997; RIFM, 1998; RIFM, 1999; Letizia, 2003; RIFM, 1978a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 52.84% (OECD 301D)	(ECHA REACH Dossier: Methyl N-methylanthranilate; ECHA, 2016)
Bioaccumulation:	
Screening-level: 33.3 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-h algae EC50: 5.284 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 96-h algae EC50: 5.284 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.5284 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** Methyl N-methylanthranilate
2. **CAS Registry Number:** 85-91-6
3. **Synonyms:** Benzoic acid, 2-(methylamino)-, methyl ester; Dimethyl anthranilate; 2-Methylamino methyl benzoate; N-Methylanthranilic acid, methyl ester; Methyl o-methylaminobenzoate; Methyl 2-methylaminobenzoate; N-アルキル(C = 1–4)-o-アミノ安息香酸アルキル; Methyl 2-(methylamino)benzoate; Methyl N-methylanthranilate
4. **Molecular Formula:** $C_9H_{11}NO_2$
5. **Molecular Weight:** 165.19
6. **RIFM Number:** 540
7. **Stereochemistry:** Isomer not specified. One stereocenter at the nitrogen and 2 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 256 °C (Fragrance Materials Association [FMA]), 249.86 °C (EPI Suite)
2. **Flash Point:** 195 °F; CC (FMA), 91 °C (Globally Harmonized System)
3. **Log K_{OW}:** 2.81 (EPI Suite)
4. **Melting Point**: 18.5–19.5 °C (Fenaroli), 42.1 °C (EPI Suite)
5. **Water Solubility:** 257 mg/L (EPI Suite)
6. **Specific Gravity:** 1.128–1.134 (FMA), 1.128 (FMA), 1.126–1.132 (FMA)
7. **Vapor Pressure:** 0.0131 mm Hg at 20 °C (EPI Suite v4.0), 0.01 mm Hg at 20 °C (FMA), 0.0208 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Absorbs between 290 and 700 nm, with peak absorbance at 350 nm and returning to baseline by 410 nm; molar absorption coefficient (6120 L • mol-1 • cm^{-1}, condition not specified) is above the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Pale yellow liquid with bluish fluorescence, grape-like odor. May crystallize. Musty-floral, sweet, and rather heavy. Orange-blossom-mandarin-peel-like odor. Winey fruity undertones (Arctander, Volume II, 1969).

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.013% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0083 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00046 mg/kg/day (RIFM, 2019)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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 (RIFM, 2015a; Safford, 2015; Safford, 2017; and Comiskey, 2017).

5. Derivation of systemic absorption

1. **Dermal:** 29.3%

RIFM, 2014: A study was designed to determine the *in vitro* human skin permeation rate and distribution of dimethyl anthranilate (DMA). Application (5 μL/cm^2 containing 15 μg/cm^2) was in 70/30 (v/v) ethanol/water under both unoccluded and occluded conditions. Twelve active dosed diffusion cells were prepared (using 4 donors) for both unoccluded and occluded conditions plus 4 control cells (1 per donor, unoccluded). Epidermal membranes (from female breast and abdominal skin obtained from cosmetic surgery and stored at −20 °C and thawed at room temperature for processing) were used and integrity was assessed by measuring electrical resistance. Permeation of DMA from a 5 μL/cm^2 dose of a 0.302% (w/v) solution in 70% ethanol was then measured at 12 time points over 24 h, using a pH 7.4 phosphate-buffered saline receptor phase. For the occluded group, chambers were occluded using greased glass coverslips applied immediately following application. At 24 h, the epidermal membranes were wiped, tape stripped 10 times, and the DMA content of the wipes, strips, and remaining epidermis was determined. Filter paper skin supports were extracted, and diffusion cell donor chambers and glass coverslips (for the occluded group) were wiped to remove sealing grease and then washed. These samples were analyzed so that mass balance could be performed. Evaporative loss of DMA was estimated by measuring the loss from PTFE sheets under the same conditions. Sensitive UHPLC-UV methods were developed for both DMA and its hydrolysis product, methyl anthranilate (MA). Hydrolysis of DMA was not a significant issue; MA was only found at very low concentrations in later time point samples in some receptor phase samples. It was not found in any skin distribution samples. At 24 h, 2.4 ± 0.19 and 4.12 ± 0.22 μg/cm^2 parent DMA (comprising DMA + MA) had permeated under unoccluded and occluded conditions, respectively, corresponding to 15.9 ± 1.3 and 27.3 ± 1.4% of the applied dose. Overall recoveries of the applied DMA were relatively low at 24.5 ± 1.7 and 59.7 ± 1.2% of the dose for unoccluded and occluded conditions, respectively. The investigation of evaporative loss from PTFE sheets mounted in diffusion cells showed that evaporation was rapid (<5% recovered at 2 h). The overall skin absorption values, defined as amounts that have permeated and amounts in the epidermis (therefore excluding tape strips) and skin support, were 2.62 ± 0.21 and 4.42 ± 0.23 μg/cm^2, for the unoccluded and occluded groups respectively, corresponding to 17.4 ± 1.4 and 29.3 ± 1.5% of the applied dose.

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

6. Computational toxicology evaluation

6.1. *Cramer Classification*

Class II, Intermediate* (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	III	II

*See the Appendix below for further details.

6.2. *Analogs Selected*

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** Methyl anthranilate (CAS # 134-20-3)
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. *Read-across Justification*

See Appendix below

7. Metabolism

Yamaori (2005): Male Hartley strain guinea pigs (8 weeks old) were euthanized, and liver microsomes and cytosol fractions were prepared. The test material methyl N-methylanthranilate was incubated with guinea pig liver microsomes (5 μg protein) or cytosol (50 μg protein) and incubated for 5 min. After the termination of the reaction, the supernatant was injected onto an HPLC system to determine the formation of methyl-N-methyl anthranic acid. The oxidative activity of the microsomes toward the test material was determined by incubating it with guinea pig liver microsomes, NADPH-generating system, and glucose 6-phosphate dehydrogenase. The mixture was incubated at 37 °C for 5 min, and the reaction was then terminated and centrifuged. The organic layer was analyzed by HPLC. The test material was hydrolyzed to N-methyl anthranilic acid, and the formation of the metabolite did not require an NADPH-generating system. The methyl-N-methyl anthranilate and N-methyl anthranilic acid were oxidized by the liver

microsomes to methyl anthranilate and anthranilic acid, respectively, in the presence of an NADPH-generating system.

To determine the kinetic parameters for the hydrolysis of test material, the liver microsomes and cytosol from guinea pigs were incubated with methyl-N-methylanthranilate under the same conditions as described above. The results showed that the hydrolytic activity for methyl-N-methylanthranilate was 18-fold higher in the liver microsomes than the cytosol, and the liver microsomal activity for methyl-N-methylanthranilate was 13-fold greater than that of methyl-N-methyl N-demethylation. The oxidation of N-methyl anthranilic acid in liver microsomes was 1.4-fold greater than that of the methyl-N-methylanthranilate. The V_{max} values for hydrolytic reactions were 30-fold greater in the liver microsomes than in the liver cytosol. Also, the Km values for methyl-N-methylanthranilate hydrolysis by liver microsomes were 4.3-fold greater than that of the cytosol. Thus, the V_{max}/K_m values reflecting the intrinsic clearance for hydrolysis were 7.4-fold greater in the microsomes than in the cytosol, respectively. The proposed metabolic pathway is as given below (Fig. 1).

Additional References: None.

8. Natural occurrence

Methyl N-methylanthranilate is reported to occur in the following foods by the VCF*:

Citrus fruits
Honey
Mangifera species
Starfruit (*Averrhoa carambola* L.)

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

9. REACH dossier

Available; accessed 10/04/21 (ECHA, 2016).

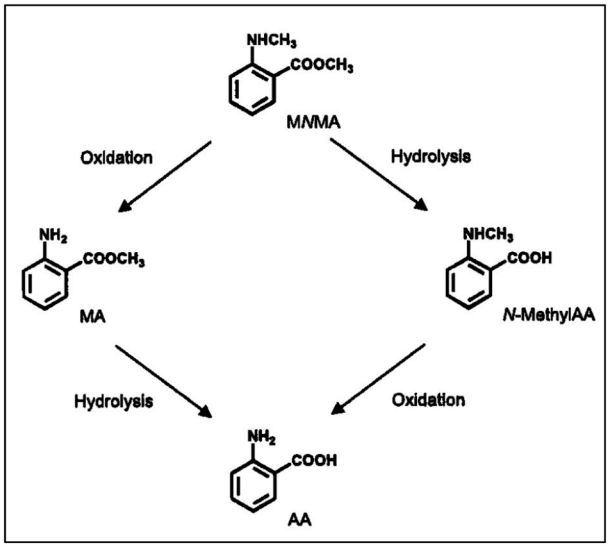


Fig. 1. Adapted from Yamaori et al (2005).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for methyl N-methylanthranilate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.10
2	Products applied to the axillae	0.10
3	Products applied to the face/body using fingertips	0.10
4	Products related to fine fragrances	0.10
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.10
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.10
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.10
5D	Baby cream, oil, talc	0.10
6	Products with oral and lip exposure	0.10
7A	Products applied to the hair with some hand contact	0.50
7B	Products with significant ano-genital exposure (tampon)	0.10
8	Products with significant ano-genital exposure (tampon)	0.10
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.50
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.50
10B	Aerosol air freshener	0.10
11A	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate without UV exposure	No Restriction
11B	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate with potential UV exposure	0.10
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For methyl N-methylanthranilate, the basis was a reference dose of 2.44 mg/kg/day, a phototoxicity NOEL of 0.5% (Maximum Acceptable Concentration = 0.1%), and a measured skin absorption value of 29.3%.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the data and current use levels, methyl N-methylanthranilate does not present a concern for genotoxic potential.

11.1.1.1. Risk assessment. Methyl N-methylanthranilate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2015c). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

Methyl N-methylanthranilate was assessed for its ability to induce mutations in a GLP bacterial reverse mutation study in accordance with OECD TG 471 using the plate incorporation and preincubation methods. *S. typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with methyl N-methylanthranilate in dimethyl sulfoxide (DMSO) at concentrations of 3, 10, 33, 100, 333, 1000, 3330, and 5000 μg/plate in the presence and absence of metabolic activation. The test material did not produce significant increases in revertant colony numbers in any of the 5 tester strains either in the presence or absence of metabolic activation and was considered not mutagenic (RIFM, 2003).

The clastogenicity of methyl N-methylanthranilate was assessed in an *in vitro* MNT assay conducted in compliance with GLP regulation and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with methyl N-methylanthranilate in DMSO at concentrations up to 300 μg/mL in the presence or absence of metabolic activation. No significant increase in the percentage of micronucleated binucleated cells was detected (RIFM, 2015b). Under the conditions of the study, methyl N-methylanthranilate was considered not clastogenic in human peripheral blood lymphocytes.

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

Additional References: Yoshimi (1988).

Literature Search and Risk Assessment Completed On: 03/10/21.

11.1.2. Repeated dose toxicity

The MOE for methyl N-methylanthranilate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on methyl N-methylanthranilate. A 13-week dietary study conducted on a group of 15 CFE rats/sex/group was administered methyl N-methylanthranilate at doses of 0, 300, 1200, or 3600 ppm (equivalent to 0, 21, 82, or 244 mg/kg/day in males and 0, 24, 95, or 280 mg/kg/day in females). There were no toxicologically relevant adverse effects reported among the animals up to the highest dose tested. The NOAEL was determined to be 3600 ppm or 244 mg/kg/day for males and 280 mg/kg/day for females (Gaunt, 1970). In another study, a group of 15 FDRL rats/sex/group were administered methyl N-methylanthranilate for 90 days at doses of 19.9 and 22.2 mg/kg/day in males and females, respectively via the diet. There were no adverse effects reported up to the highest dose tested (Oser, 1965, data also available in Bar, 1967). As stated in Section VII, methyl N-methylanthranilate is expected to hydrolyze to N-methyl anthranilic acid and later oxidize to anthranilic acid (CAS # 118-92-3), or it is expected to oxidize to methyl anthranilate (CAS # 134-20-3) and later hydrolyze to anthranilic acid. A dietary chronic carcinogenicity study conducted on anthranilic acid did not show any evidence of carcinogenicity among rats and mice up to the highest dose tested in either species (rats: 30000 ppm and mice: 50000 ppm) (NCI, 1978). Also, there is sufficient repeated dose toxicity data on metabolite methyl anthranilate. A dietary 90-day subchronic toxicity study was conducted in rats. Groups of 10 weanling Osborne-Mendel rats per sex were administered methyl anthranilate in the diet for 13 weeks at 0, 1000, and 10000 ppm (equivalent to 0, 50, and 500 mg/kg/day). There were no test material-related adverse effects reported up to the highest dose tested. The NOAEL was determined to be 10000 ppm or 500 mg/kg/day (Hagan, 1967). The overall NOAEL for repeated dose toxicity endpoint for methyl N-methylanthranilate was determined to be 244 mg/kg/day. A dermal absorption study conducted on human skin on methyl N-methyl anthranilate resulted in a 29.3% skin absorption value (RIFM, 2014; see Section V).

Therefore, the methyl N-methylanthranilate MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl N-methylanthranilate NOAEL in mg/kg/day by the total systemic exposure to methyl N-methylanthranilate, 244/0.00046 or 530434.

In addition, when correcting for skin absorption (see Section V), the total systemic exposure to methyl N-methylanthranilate (0.46 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1.1. Derivation of reference dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account phototoxicity and a reference dose of 2.44 mg/kg/day.

The reference dose for methyl N-methyl anthranilate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 244 mg/kg/day by the uncertainty factor, 100 = 2.44 mg/kg/day.

*The Expert Panel for fragrance safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: Oser (1965); Bar (1967); Clark (1980); RIFM, 1963; Yamaori (2005); Dahl (1983); RIFM, 1974b; Grundschober (1977); Hagan (1967); Stoner (1973); Cutting (1966).

Literature Search and Risk Assessment Completed On: 02/01/21.

11.1.3. Reproductive toxicity

The MOE for methyl N-methylanthranilate is adequate for the developmental toxicity endpoint at the current level of use.

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

11.1.3.1. Risk assessment. The developmental toxicity data on methyl N-methylanthranilate are insufficient for the developmental toxicity endpoint. Metabolite methyl anthranilate (CAS # 134-20-3; see Section VI) 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 bodyweight 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 bodyweight gains), no effects of any of the investigated developmental parameters were observed. 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). A dermal absorption study conducted on human skin on methyl N-methyl anthranilate resulted in a 29.3% skin absorption value (RIFM, 2014; see Section V).

Therefore, the methyl N-methylanthranilate 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-methylanthranilate, 768.4/0.00046 or 1670435.

In addition, when correcting for skin absorption, the total systemic exposure to methyl N-methylanthranilate (0.46 μg/kg/day) is below the TTC (9 μg/kg/day) for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

There are no fertility data on methyl N-methylanthranilate or any read-across materials that can be used to support the reproductive toxicity endpoint. An *in vitro* skin absorption study was conducted with methyl N-methylanthranilate using human skin. Under the more severe condition of occlusion, 29.3% of the applied dose was absorbed (RIFM, 2014). When correcting for skin absorption, the total systemic exposure to methyl N-methylanthranilate (0.46 μg/kg/day) is below the TTC (9 μg/kg/day) for the fertility endpoint of a Cramer Class II material at the current level of use.

Additional References: Oser (1965); Bar (1967); Clark (1980);

RIFM, 1963; Yamaori (2005); Dahl (1983); RIFM, 1974b; Grundschober (1977); Hagan (1967); Stoner (1973); Cutting (1966).

Literature Search and Risk Assessment Completed On: 03/10/21.

11.1.4. Skin sensitization

Based on the available data, methyl N-methylanthranilate does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the available data, methyl N-methylanthranilate does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In guinea pig tests, no reactions indicative of sensitization were observed (Klecak, 1977, 1985). In a human maximization test, 2 reactions were observed with 10% (6900 μg/cm^2) methyl N-methylanthranilate in petrolatum on a panel of 25 subjects; however, these were considered questionable due to the presence of concurrent test materials for which numerous strong reactions were observed (RIFM, 1974a). The human maximization test was repeated using the same concentration, and no reactions (0/25) indicative of sensitization were observed (RIFM, 1974a).

Based on the weight of evidence (WoE) from structural analysis, animal data, and human studies, methyl N-methylanthranilate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: Yamaori (2005).

Literature Search and Risk Assessment Completed On: 02/23/21.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorbance spectra and the available study data, methyl N-methylanthranilate has a phototoxic potential. Based on human studies, it does not present a risk for photoallergenicity.

11.1.5.1. Risk assessment. Based on the UV/Vis absorbance spectra and available study data, methyl N-methylanthranilate has phototoxic potential. The available UV absorption spectrum for methyl N-methylanthranilate demonstrates that this material absorbs in the region of 290–700 nm, with a peak absorbance at 350 nm and returning to baseline by 410 nm. The molar absorption coefficient (6120 L mol^{-1} • cm^{-1}) for peak absorbance between 290 and 700 nm is above the benchmark of concern for phototoxic effects (Henry, 2009). Methyl N-methylanthranilate was determined to be phototoxic in both the 3T3 Neutral Red Uptake (NRU) phototoxicity assay and a 3D human skin model (Skin2™) phototoxicity assay (RIFM, 1997; RIFM, 2002). In other 3T3 NRU studies conducted with diluted test material, 0.01%, 0.05%, and 0.1% methyl N-methyl anthranilate were not predicted to be phototoxic (RIFM, 2010c; RIFM, 2010b; RIFM, 2010a). In mice, phototoxic effects were observed when methyl N-methylanthranilate was tested at 50% and 100% (RIFM, 1978b). In humans, phototoxic effects have generally been observed at concentration ranging from 1% to 5% (RIFM, 1999; RIFM, 1978a; Kaidbey, 1980; Letizia, 2003). The no observed effect level for phototoxic effects in humans is 0.5% (RIFM, 1998). Considering a safety factor for phototoxicity of 5, the maximum acceptable concentration based on phototoxicity alone for methyl N-methylanthranilate is 0.1%. While phototoxicity has been observed to methyl N-methylanthranilate, no photoallergic responses have been reported up to the maximum tested concentration of 5% (RIFM, 1978a). Based on these data, methyl N-methylanthranilate has phototoxic potential, with a maximum acceptable concentration of 0.1% based on phototoxicity alone. Maximum acceptable concentrations across all finished product categories and all endpoints may be found in Section X. Based on human studies; it does not present a risk for photoallergenicity.

11.1.5.2. UV spectra analysis. The available UV absorption spectrum for methyl N-methylanthranilate demonstrates that this material absorbs in the region of 290–700 nm, with peak absorbance at 350 nm and returning to baseline by 410 nm. The molar absorption coefficient (6120 L mol^{-1} • cm^{-1})for peak absorbance between 290 and 700 nm is above the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/12/21.

11.1.6. Local respiratory toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on methyl N-methylanthranilate. Based on the Creme RIFM Model, the inhalation exposure is 0.0083 mg/day. This exposure is 56.6 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methyl N-methylanthranilate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, Methyl N-methylanthranilate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified methyl N-methylanthranilate as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above

screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), methyl N-methylanthranilate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. Not available.

11.2.2.1.2. Ecotoxicity. Not available.

11.2.2.1.3. Other available data. Methyl N-methylanthranilate has been registered for REACH with the following additional data available (ECHA, 2016):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 52.84% was observed after 42 days.

The acute fish (*Danio rerio*) toxicity test was conducted according to the OECD 203 guideline under static conditions. The 96-h LC50 value based on nominal test concentration was reported to be > 12.5 mg/L but <25 mg/L.

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 72-h EC50 value based on measured concentration was reported to be 43.2 mg/L (95% CI: 26.8–69.4 mg/L).

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 value based on measured concentration for growth rate was reported to be 111.7 mg/L (95% CI: 88.2–141.4 mg/L).

11.2.3. Risk assessment refinement

Since Methyl N-methylanthranilate has passed the screening criteria, 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.81	2.81
Biodegradation Factor Used	0.1	0.1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
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 0.5284 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 03/04/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	43.98			1000000	0.04398	
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	7.410	14.121	5.284	10000	0.5284	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	25.30	15.48	15.73			Neutral Organics SAR

- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:**

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 10/04/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112777.

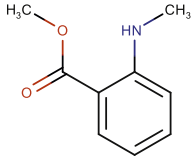
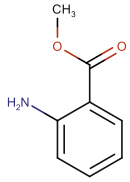
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Methyl N-methylanthranilate	Methyl anthranilate
CAS No.	85-91-6	134-20-3
Structure		
Similarity (Tanimoto Score)		0.86
Endpoint		Developmental toxicity
Molecular Formula	$C_9H_{11}NO_2$	$C_8H_9NO_2$
Molecular Weight	165.192	151.165
Melting Point (°C, EPI Suite)	19.00	24.50
Boiling Point (°C, EPI Suite)	255.00	256.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.77E+00	3.61E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.57E+02	2.85E+03
Log KOW	2.81	1.88

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
J_{max} (μg/cm^2/h, SAM)	12.97	50.58
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.73E-03	1.92E-01
Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group	Weak binder, NH2 group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (low reliability)	Toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There is insufficient toxicity data on methyl N-methylanthranilate (CAS # 85-91-6). Hence *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, methyl anthranilate (CAS # 134-20-3) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- Methyl anthranilate (CAS #134-20-3) is used as a read-across analog for methyl N-methylanthranilate (CAS # 85-91-6) for the developmental toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of anthranilates.
  - o The target material and the read-across analog have methyl anthranilate common among them.
  - o The key difference between the target material and the read-across analog is that the target is an N-methylated secondary amine while the read-across is a primary amine. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The target material and the read-across analog have similar physical–chemical properties. Differences in some of the physical–chemical properties of the target material and the read-across analog are toxicologically insignificant for the reproductive toxicity endpoint.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have an alert of toxicant and weak ER binder by *in silico* models. The data on the read-across analog confirm that the MOE is adequate under the current level of use. Therefore, based on the structural similarity between the read-across analog and the target material and the data on the read-across analog, the *in silico* alerts are superseded by the data.
  - o The structural alerts for reproductive toxicity are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant.

Explanation of Cramer Classification

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
Q7. Heterocyclic? No
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation) No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? Yes
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 ($n \geq 4$) on the aromatic or aliphatic side chain? No 'Residue 1'
Q22. A common component of food? No
Q33. Has a 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'
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 ($n \geq 4$) on the aromatic or aliphatic side chain? No 'Residue 1'
Q22. A common component of food? No 'Residue 1'
Q33. Has a 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 2'
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No 'Residue 2'

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? Yes 'Residue 2' Class Intermediate (Class II)

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