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RIFM fragrance ingredient safety assessment, benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester, CAS Registry Number 14735-72-9

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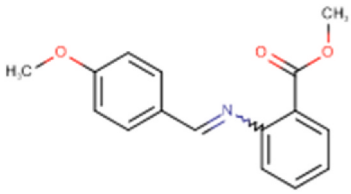

Name: Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester CAS Registry Number: 14735-72-9

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Abbreviation/Definition List:

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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., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
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 et al., 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. This material has not been fully evaluated for photoallergenic potential.

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Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The photoirritation endpoint was evaluated based on exposure; benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester is not expected to be photoirritating. Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]- was not evaluated for photoallergenicity. The environmental endpoints were evaluated; for the hazard assessment based on the screening data, benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester was not able to be risk screened as there were no reported volumes of use (VoU) for either North America or Europe in the 2019 IFRA Survey.

Human Health Safety Assessment
Genotoxicity: Not genotoxic (RIFM, 2017a; RIFM, 2017b)
Repeated Dose Toxicity: No NOAEL is available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL is available. Exposure is below TTC.
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
Photoirritation/Photoallergenicity: Not a concern for photoirritation under the declared use levels. Photoallergenicity has not been evaluated.
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence:
Screening-level: 2.7 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 52 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Not applicable

Risk Assessment:
- Not Applicable; no 2019 VoU reported

1. Identification

1. **Chemical Name:** Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester
2. **CAS Registry Number:** 14735-72-9
3. **Synonyms:** Anisimea; Methyl 2-[(4-methoxybenzylidene)amino]benzoate; Benzoic acid, 2-.(.(.(4-methoxyphenyl)methylene.).amino.).-,methyl ester
4. **Molecular Formula:** Not Available
5. **Molecular Weight:** 269.3 g/mol
6. **RIFM Number:** 6503
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 372.07 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.12 (EPI Suite)
4. **Melting Point**: 120.21 °C (EPI Suite)
5. **Water Solubility:** 40.12 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00000212 mm Hg at 20 °C (EPI Suite v4.0), 4.46e-006 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with a peak at 290 nm and returning to baseline by 370 nm. Molar absorption coefficients (12441, 11438, and 7649 L mol^{-1} • cm^{-1} under

neutral, acidic, and basic conditions, respectively) are above the benchmark (1000 L $mol^{-1} \bullet cm^{-1}$)
9. **Appearance/Organoleptic:** Not available

3. Volume of use (Worldwide band)

1. No VoU reported in 2019 (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95th Percentile Concentration in Deodorant Spray:** 0.000000086% (RIFM, 2016)

   (No reported use in fine fragrance).

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** <0.0001 mg/kg/day (RIFM, 2016)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class III, High.

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

6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester is not reported to occur in foods by the VCF*.

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

9. REACH dossier

Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester has been pre-registered for 2010; no dossier available as of 01/31/22.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester 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, 2013). 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.

The mutagenic activity of benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. While no increases were observed in the initial study, a ≥2-fold increase in the mean number of revertant colonies was observed in strain WP2uvrA at 16.0 and 100 μg/plate in the presence of an S9 activation system in only the confirmatory study (RIFM, 2017a). To confirm this result, an additional confirmatory study was conducted with WP2uvrA in the presence of S9 at concentrations up to 500 μg/plate. No increases in the frequency of revertant mutations were observed in the confirmatory study. Due to the lack of reproducibility and concentration-related increases, the ≥2-fold increase observed in the second study was considered to be not biologically relevant. Under the conditions of the study, benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester was not mutagenic in the Ames test.

The clastogenic activity of benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester 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 benzoic acid, 2-(((4-methoxyphenyl)methylene)amino)-, methyl ester in DMSO at concentrations up to 1000 μg/mL in the DRF study; micronuclei analysis was conducted at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation. Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester did not

induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, benzoic acid, 2-[[(4-methoxyphenyl) methylene]amino]-, methyl ester does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/21/22.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester or any read-across materials. The total systemic exposure to benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester (0.1 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/13/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester or any read-across materials. The total systemic exposure to benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester (0.1 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/13/22.

11.1.4. Skin sensitization

Based on the existing data, benzoic acid, 2-[[(4-methoxyphenyl) methylene]amino]-, methyl ester is a sensitizer. However, it does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester (Table 1). The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). A guinea pig Buehler test presented reactions indicative of sensitization (RIFM, 1992). However, in a Confirmation of No Induction in Humans test (CNIH) with 1000 μg/cm^2 of benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester in SDA-39C, no reactions indicative of sensitization were observed in any of the 54 volunteers (RIFM, 1983). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts et al., 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 2 provides the supported concentrations for benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent supported concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/06/22.

11.1.5. Photoirritation/photoallergenicity

Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester demonstrates significant absorbance in the UV/Vis light range (290–700 nm) making it a concern for photosafety. However, based on the highest dermal 95th percentile concentration data, benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester would not be

Table 1
Summary of existing data on benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
Sensitizer; Human potency category unknown; Current exposure level below the DST for reactive materials.	1000	NA	NA	NA	NA	NA	Positive
	***In vitro* Data[f]**				***In silico* protein binding alerts (OECD Toolbox v4.2)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	NA	NA	NA		No alert found	No alert found	Schiff base formation

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[e] Studies conducted according to the OECD TG 406 are included in the table.

[f] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

Table 2
Supported concentrations for benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester that present no appreciable risk for skin sensitization based on reactive DST.

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

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] These levels represent supported concentrations based on the DST. However, additional studies may show it could be used at higher levels.
[c] No reported use.
[d] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

expected to present a concern for photoirritation under the current, declared levels of use. Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester was not evaluated for photoallergy. However, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester.

11.1.5.1. Risk assessment. There are no photoirritation studies available for benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester in experimental models. UV/Vis absorption spectra indicate significant absorption between 290 and 700 nm. The corresponding molar absorption coefficients are above the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester presents a concern for photoirritation and photoallergenicity based on significant UV/Vis absorbance. However, the highest 95th percentile dermal concentration among all photoirritation-applicable product categories was found in Category 2 and was 0.00000032%. This level is below the maximum acceptable concentration for leave-on cosmetics (0.0005%) set for furocoumarins, a potent class of photoirritants; this value is used as an exposure limit, below which it is unlikely that any type of photoirritating potential exists (Api et al., 2015). Significant absorbance of benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester in the UV/Vis range makes it a concern for photosafety. However, based on the highest dermal 95th percentile concentration data, benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester would not be expected to present a concern for photoirritation under the current, declared levels of use. Benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester was not evaluated for photoallergy; RIFM is sponsoring an *in vitro* photoallergy research program to evaluate its photoallergy potential.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate significant absorbance between 290 and 700 nm, with a peak at 290 nm and returning to baseline by 370 nm. Molar absorption coefficients (12441, 11438, and 7649 L $mol^{-1} \bullet cm^{-1}$ under neutral, acidic, and basic conditions, respectively) are above the benchmark of concern for photoirritating effects, 1000 L $mol^{-1} \bullet cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/18/22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester 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 benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 4700 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/19/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester was performed following the RIFM Environmental Framework (Salvito et al., 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional

tonnage, not the extremes of the range. Following the RIFM Environmental Framework, benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester was not assessed as no VoU has been reported.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017). 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

Not applicable.

11.2.2.1. Key studies. ***Biodegradation:***

No data available.

Ecotoxicity:

No data available.

Other available data:

benzoic acid, 2-[[(4-methoxyphenyl)methylene]amino]-, methyl ester has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Not applicable.

Literature Search and Risk Assessment Completed On: 06/15/22.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 06/20/22.

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.

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