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Short Review

RIFM fragrance ingredient safety assessment, ethyl *p*-anisate, CAS registry number 94-30-4

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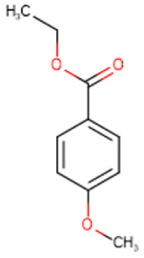
Name: Ethyl *p*-anisate



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CAS Registry Number: 94-30-4

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., 2021)

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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., 2015; Safford 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.

Ethyl *p*-anisate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs 4-methoxybenzoic acid (CAS # 100-09-4) and ethyl alcohol (CAS # 64-17-5) show that ethyl *p*-anisate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to ethyl *p*-anisate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; ethyl *p*-anisate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; ethyl *p*-anisate 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 (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2016b; RIFM, 2016c; ECHA, 2011)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL 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 photoirritating/photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 2016a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 2.8 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 17.8 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 108.9 mg/L (RIFM Framework; Salvito, 2002)
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: Fish LC50: 108.9 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.1089 μg/L
- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Ethyl *p*-anisate
2. **CAS Registry Number:** 94-30-4
3. **Synonyms:** Benzoic acid, 4-methoxy-, ethyl ester; Ethyl anisate; Ethyl *p*-methoxybenzoate; Ethyl 4-methoxybenzoate; Ethyl *p*-anisate
4. **Molecular Formula:** $C_{10}H_{12}O_3$
5. **Molecular Weight:** 180.2 g/mol
6. **RIFM Number:** 623
7. **Stereochemistry:** No stereocenters are present, and no stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 270 °C (Fragrance Materials Association [FMA]), 252.81 °C (EPI Suite)
2. **Flash Point:** >200 °F; closed cup (FMA)
3. **Log K_{OW}:** 2.4 (EPI Suite)
4. **Melting Point:** 33.38 °C (EPI Suite)
5. **Water Solubility:** 489.9 mg/L (EPI Suite)
6. **Specific Gravity:** 1.10 (FMA)
7. **Vapor Pressure:** 0.00583 mm Hg at 20 °C (EPI Suite v4.0), 0.008 mm Hg at 20 °C (FMA), 0.00949 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm under the biologically relevant neutral condition; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1}). Significant absorbance between 290 and 700 nm under acidic and basic conditions, with peak absorbance at 290 nm and returning to baseline by 330 nm. Molar absorbances (2079 and 2462 L mol^{-1} • cm^{-1} for acidic and basic conditions, respectively) are above the benchmark (1000 L mol^{-1} • cm^{-1}).

9. **Appearance/Organoleptic:** A colorless, oily liquid that has a sweet-floral, anisic-fennel-like, mild odor with a resemblance to chervil, hawthorn flowers, anise, and fennel.

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00019% (RIFM, 2020)
2. **Inhalation Exposure*:** 0.0000026 mg/kg/day or 0.00015 mg/day (RIFM, 2020)
3. **Total Systemic Exposure**:** 0.00012 mg/kg/day (RIFM, 2020)

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
I	I	I

6.2. Analogs selected

a. **Genotoxicity:** 4-Methoxybenzoic acid (CAS # 100-09-4) and ethyl alcohol (CAS # 64-17-5)
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

6.3. Read-across justification

See Appendix below.

7. Metabolism

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

8. Natural occurrence

Ethyl *p*-anisate is reported to occur in the following foods by the VCF*:

Apple brandy (*Calvados*).
Feyoa fruit (*Feijoa sellowiana*).
Guava and feyoa.
Japanese plum (*Prunus salicina lindl cultivars*).
Plum (*Prunus* species).
Starfruit (*Averrhoa carambola* L.)
White wine.
Wine.

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

9. REACH dossier

Ethyl *p*-anisate has been pre-registered for 2010; no dossier available as of 01/31/23.

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, ethyl *p*-anisate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Ethyl *p*-anisate 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, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of ethyl *p*-anisate; however, read-across can be made to 4-methoxybenzoic acid (CAS # 100-09-4; see Section VI) and ethyl alcohol (CAS # 64-17-5; see Section VI).

The mutagenic activity of read-across material 4-methoxybenzoic acid 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 4-methoxybenzoic acid in dimethyl sulfoxide (DMSO) 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, 2016b). Under the conditions of the study, 4-methoxybenzoic acid was not mutagenic in the Ames test, and this can be extended to ethyl *p*-anisate.

The mutagenic activity of ethyl alcohol has been evaluated in a bacterial reverse mutation assay conducted in an equivalent manner to OECD TG 471 (ECHA, 2011). Under the conditions of the study, ethyl alcohol was not mutagenic in the Ames test, and this can be extended to ethyl *p*-anisate.

The clastogenic activity of read-across material 4-methoxybenzoic acid 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 4-methoxybenzoic acid in DMSO at concentrations up to 1522 μg/mL in the presence and absence of S9 for 3 and 24 h. No statistically significant increase in the MNBN frequencies was observed at any evaluated concentrations in any treatment condition with or without S9 (RIFM, 2016c). Under the conditions of the study, 4-methoxybenzoic acid was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to ethyl *p*-anisate.

The clastogenic activity of ethyl alcohol was evaluated in an *in vitro* micronucleus test conducted in accordance with OECD TG 487 (ECHA, 2011). Under the conditions of the study, ethyl alcohol was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to ethyl *p*-anisate.

Based on the available data, 4-methoxybenzoic acid and ethyl alcohol do not present a concern for genotoxic potential, and this can be extended to ethyl *p*-anisate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/19/22.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on ethyl *p*-anisate or any read-across materials. The total systemic exposure to ethyl *p*-anisate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on ethyl *p*-anisate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to ethyl *p*-anisate (0.12 μg/kg/day) is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material (30 μg/kg/day; Kroes et al., 2007) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/04/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on ethyl *p*-anisate or any read-across materials. The total systemic exposure to ethyl *p*-anisate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on ethyl *p*-anisate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to ethyl *p*-anisate (0.12 μg/kg/day) is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/04/22.

11.1.4. Skin sensitization

Based on existing data and the application of DST, ethyl *p*-anisate does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for ethyl *p*-anisate (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 v4.5). In a human maximization test, no skin sensitization reactions were observed at 2760 μg/cm^2 (RIFM, 1975). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford, 2011; Roberts et al., 2015; Safford, 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 2 provides the supported concentrations for ethyl *p*-anisate that present no appreciable risk for skin sensitization based on the non-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: 07/18/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra and *in vitro* study data, ethyl *p*-anisate would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, ethyl *p*-anisate does not present a concern for photoallergy.

11.1.5.1. Risk assessment. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the critical range of 290–700 nm under neutral conditions and significant absorbance under acidic and basic conditions, with peak absorbance at 290 nm and returning to baseline by 330 nm. The corresponding molar absorption coefficients are above the benchmark of concern for photoirritation/photoallergenicity (Henry et al., 2009). However, the acidic and basic conditions in this assay are defined as pH 2 or less and pH10 or greater, respectively, and are not biologically relevant for our purposes, where the route of exposure is topical. In a 3T3-Neutral Red Uptake photoirritation test, ethyl *p*-anisate was not predicted to have photoirritating potential (RIFM, 2016a). Based on the available UV/Vis absorption spectra and *in vitro* study data, ethyl *p*-anisate would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra at the biologically relevant neutral condition, ethyl *p*-anisate does not present a concern for photoallergy.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were generated for ethyl *p*-anisate. The spectra demonstrate that the material does not absorb in the range of 290–700 nm under the biologically relevant neutral condition. Significant absorbance was observed under acidic and basic conditions. Corresponding molar absorption coefficients were 2079 and 2462 L mol^{-1} • cm^{-1} under acidic and basic conditions, respectively, which are above 1000 L mol^{-1} • cm^{-1}, the benchmark of concern for photoirritating/photoallergenic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/26/22.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for ethyl *p*-anisate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on ethyl *p*-anisate. Based on the Creme RIFM Model, the inhalation exposure is 0.00015 mg/day. This exposure is 9333.4 times lower than the Cramer Class I TTC value of 1.4 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: 07/13/22.

Table 1
Summary of existing data on ethyl *p*-anisate.

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]
Human potency category unknown; Current exposure level below the DST for non-reactive materials.	NA	2760	NA	NA	NA	NA	NA
	***In vitro* Data[f]**				***In silico* protein binding alerts (OECD Toolbox v4.5)**		
	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.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl *p*-anisate 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 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, ethyl *p*-anisate 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 EPI Suite v4.11 (US EPA, 2012a) did not identify ethyl *p*-anisate as possibly being 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). 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 ≥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 VoU (2019), ethyl *p*-anisate does not present a risk to the aquatic compartment in the screening-level assessment.

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

No data available.

Ecotoxicity:

No data available.

Other available data:

Ethyl *p*-anisate has been pre-registered for REACH with no additional data at this time.

11.2.3. 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.

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

Exposure	Europe	North America
Log K_{ow} Used	2.4	2.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.1089 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: 07/27/22.

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/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	108.9	N/A	N/A	1000000	0.1089	N/A

Table 2
Supported concentrations for ethyl *p*-anisate that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Supported Concentrations[b] (%) in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069	1.1×10^{-6}
2	Products applied to the axillae	0.021	0.0015
3	Products applied to the face using fingertips	0.41	4.4×10^{-4}
4	Fine fragrance products	0.39	1.9×10^{-4}
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10	0.044
6	Products with oral and lip exposure	0.23	0.0022
7	Products applied to the hair with some hand contact	0.79	9.8×10^{-5}
8	Products with significant ano-genital exposure	0.041	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75	0.088
10	Household care products with mostly hand contact	2.7	3.0×10^{-4}
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	0.011

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] These levels represent maximum acceptable concentrations based on the DST. However, additional studies may show it could be used at higher levels.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

- **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 01/31/23.

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.2023.113789.

Appendix

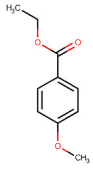
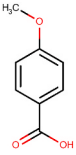
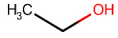
Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 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, 2017b).

- 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 (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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Ethyl *p*-anisate	4-Methoxybenzoic acid	Ethyl alcohol
CAS No.	94-30-4	100-09-4	64-17-5
Structure			
Similarity (Tanimoto Score)		0.83	0.06
SMILES	CCOC(=O)c1ccc(OC)cc1	COc1ccc(cc1)C(O) = O	CCO
Endpoint		• Genotoxicity	• Genotoxicity
Molecular Formula	$C_{10}H_{12}O_3$	$C_8H_8O_3$	C_2H_6O
Molecular Weight (g/mol)	180.203	152.149	46.069
Melting Point (°C, EPI Suite)	7.50	185.00	−114.10
Boiling Point (°C, EPI Suite)	269.50	276.50	78.20
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.27E+00	1.92E-02	7.91E+03
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.90E+02	5.30E+02	1.00E+06
Log KOW	2.4	1.96	−0.31
J_{max} (μg/cm^2/h, SAM)	9.61	10.42	7192.24
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.77E-01	6.49E-04	5.07E-01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.5)	No alert found	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	No alert found
Oncologic Classification	Not classified	Not classified	Not classified
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on ethyl *p*-anisate (CAS # 94-30-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 4-methoxybenzoic acid (CAS # 100-09-4) and ethyl alcohol (CAS # 64-17-5) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target material ethyl *p*-anisate (CAS # 94-30-4) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.5). The target material is predicted to be metabolized to 4-methoxybenzoic acid (CAS # 100-09-4) and ethyl alcohol (CAS # 64-17-5) in the first step with 0.499 pre-calculated and 0.950 intrinsic probability. Hence, 4-methoxybenzoic acid (CAS # 100-09-4) and ethyl alcohol (CAS # 64-17-5) can be used as read-across analogs for the target material. Read-across analog 4-methoxybenzoic acid (CAS # 100-09-4) and ethyl alcohol (CAS # 64-17-5) were out of domain of the training set for the *in vivo* rat and *in vitro* rat S9 simulators (OASIS TIMES v2.30.1.11). However, based on expert judgment, the model's domain exclusion was overridden, and a justification was provided.

Conclusions

- Read-across acid 4-methoxybenzoic acid (CAS # 100-09-4) and read-across alcohol ethyl alcohol (CAS # 64-17-5) were used as read-across analogs for the target ester ethyl *p*-anisate (CAS # 94-30-4) for the genotoxicity endpoint since they are hydrolysis products of the target material.

- o Structural differences between the target material and the read-across analogs are mitigated by the fact that the target material could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target material is expected to be similar to that of its metabolites.
- o The target material and the read-across analogs have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across are toxicologically insignificant.
- o According to the QSAR OECD Toolbox v4.5, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analogs.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analogs and the target material.

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