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RIFM fragrance ingredient safety assessment, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)-, CAS Registry Number 72987-59-8

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Name: Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)-CAS Registry Number: 72987-59-8

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

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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.

Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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 ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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 phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2019; RIFM, 2020a)
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.
Phototoxicity/Photoallergenicity: Not phototoxic/not expected to be photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 2017)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 91% (OECD 301F) RIFM (2013a)
Bioaccumulation:
Screening-level: 24.8 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 999.0 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: 999.0 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.999 μg/L
- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening- level

1. Identification

1. **Chemical Name:** Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)-
2. **CAS Registry Number:** 72987-59-8
3. **Synonyms:** 1-(2-Fenylethoxy)-2-(4-methylfenoxy)ethanol; 2-(4-Methylphenoxy)-1-(2-phenylethoxy)ethanol; Curgix; Curgix pure; Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)-
4. **Molecular Formula:** $C_{17}H_{20}O_3$
5. **Molecular Weight:** 272.34 g/mol
6. **RIFM Number:** 7083
7. **Stereochemistry:** One chiral center is present, and a total of 2 enantiomers are possible.

2. Physical data

1. **Boiling Point:** 385.48 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 1.2 and 1.5 (RIFM, 2013b), 3.01 (EPI Suite)
4. **Melting Point**: 128.89 °C (EPI Suite)
5. **Water Solubility:** 154.9 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 4.5e-008 mm Hg at 25 °C (EPI Suite), 1.85E-08 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm under the biologically relevant neutral condition and basic conditions; molar

absorption coefficients (210 and 215 L mol^{-1} • cm^{-1} under neutral and acidic conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1}). Significant absorbance was observed between 290 and 700 nm under acidic conditions; the molar absorption coefficient (1228 L mol^{-1} • cm^{-1}) for acidic conditions is above the benchmark of concern (1000 L mol^{-1} • cm^{-1}).

9. **Appearance/Organoleptic:** Not Available

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:** 0.0058% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.0000084 mg/kg/day or 0.00064 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.000075 mg/kg/day (RIFM, 2020b)

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

1. **Cramer Classification:** Class III, High

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

2. **Analogs Selected:**
   a. **Genotoxicity:** Weight of evidence (WoE) - phenethyl alcohol (CAS # 60-12-8)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
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

Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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

Pre-registered for 2010; no dossier available as of 05/20/22.

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, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) with and without metabolic activation, positive for genotoxicity with metabolic activation, and negative for genotoxicity without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. While the BlueScreen assay on the target material showed positive results, data from additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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 as a mixture with phenethyl alcohol (CAS # 60-12-8). *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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 concentration in the presence or absence of S9 (RIFM, 2019). Under the conditions of the study, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- was not mutagenic in the Ames test.

As additional WoE, phenethyl alcohol (CAS # 60-12-8) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 (ECHA, 2013). Under the conditions of the study, phenethyl alcohol was not mutagenic in the Ames test.

The clastogenic activity of ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487 as a mixture with phenethyl alcohol (CAS # 60-12-8). Human peripheral blood lymphocytes were treated with ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- in DMSO, and the micronuclei analysis was conducted at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation. Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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, 2020a). Under the conditions of the study, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- was considered to be non-clastogenic in the *in vitro* micronucleus test.

As additional WoE, phenethyl alcohol (CAS # 60-12-8) has been evaluated in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473 (ECHA, 2013). Under the conditions of the study, phenethyl alcohol was not mutagenic in the Ames test.

Based on the data available, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/24/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on ethanol, 2-(4-

Table 1
Summary of existing data on ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)-.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL[2] (induction) µg/cm²	WoE NESIL[3] µg/cm²	LLNA[4] Weighted Mean EC3 Value µg/cm²	GPMT[5]	Buehler[5]
Human potency category unknown; Current exposure level below the DST for reactive materials.	NA	NA	NA	NA	NA	NA	NA
	In Vitro Data[6]				*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	Michael addition; 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

[1]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).

[2]Data derived from CNIH or HMT

[3]WoE NESIL limited to 2 significant figures

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

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

methylphenoxy)-1-(2-phenylethoxy)- or any read-across materials. The total systemic exposure to ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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 ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.075 μg/kg/day) is below the TTC for ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- (1.5 μg/kg/day; Kroes et al., 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/16/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- or any read-across materials. The total systemic exposure to ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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 ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.075 μg/kg/day) is below the TTC for ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/16/21.

11.1.4. Skin sensitization

Based on the application of DST, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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 ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- (Table 1). The chemical structure of this material indicates that it would not be expected to react with skin proteins directly, while its metabolite is expected to be reactive (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). 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 ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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: 11/11/21.

11.1.5. Phototoxicity/photoallergenicity

Based on available *in vitro* study data and UV/Vis absorption spectra at the biologically relevant neutral conditions, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- would not be expected to present a concern for phototoxicity. Based on UV/Vis absorption spectra at the biologically relevant neutral conditions, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- would not be expected to present a concern for photoallergenicity.

Table 2
Supported concentrations for 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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	7.0×10^{-4}
3	Products applied to the face using fingertips	0.029	1.3×10^{-4}
4	Fine fragrance products	0.027	0.0058
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070	7.5×10^{-4}
6	Products with oral and lip exposure	0.016	NRU[c]
7	Products applied to the hair with some hand contact	0.056	5.2×10^{-4}
8	Products with significant ano-genital exposure	0.0029	No Data[d]
9	Products with body and hand exposure, primarily rinse-off	0.054	8.6×10^{-4}
10	Household care products with mostly hand contact	0.19	0.0010
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	0.038

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.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm under the biologically relevant neutral condition and under basic conditions. The corresponding molar absorption coefficients are below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Significant UV/Vis absorbance was evident under acidic conditions, and the molar absorption (1228 L mol^{-1} • cm^{-1}) was above the benchmark of concern. However, acidic conditions for the assay are defined as a pH less than 2, which is not relevant for a dermal route of exposure. In an *in vitro* 3T3 Neutral Red Uptake phototoxicity assay, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- was not predicted to have phototoxic potential, according to the prediction model presented in the OECD guidelines (RIFM, 2017). Based on available *in vitro* study data and UV/Vis absorption spectra at the biologically relevant neutral conditions, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- would not be expected to present a concern for phototoxicity. Based on UV/Vis absorption spectra

at the biologically relevant neutral conditions, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- would not be expected to present a concern for photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicated minor absorbance between 290 and 700 nm under the biologically relevant neutral condition and basic conditions; molar absorption coefficients (210 and 215 L mol^{-1} • cm^{-1} under neutral and acidic conditions, respectively) were below the benchmark (1000 L mol^{-1} • cm^{-1}) of concern for phototoxic effects. Significant absorbance was observed between 290 and 700 nm under acidic conditions; the molar absorption coefficient (1228 L mol^{-1} • cm^{-1}) for acidic conditions is above the benchmark of concern (1000 L mol^{-1} • cm^{-1}).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/22/21.

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 ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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 ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)-. Based on the Creme RIFM Model, the inhalation exposure is 0.00064 mg/day. This exposure is 734.4 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: 11/22/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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, ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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 ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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, 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 ≥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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2019), ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 2013a: The biodegradation potential of the test material was evaluated in the manometric respirometry test according to the OECD 301F method. Biodegradation of 91% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- 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 Framework: Salvito et al., 2002).

Exposure	Europe	North America
Log K_{ow} Used	1.5	1.5
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.999 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 05/19/22.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	999.0			1000000	0.999	

- **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 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
- **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 05/20/22.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113318.

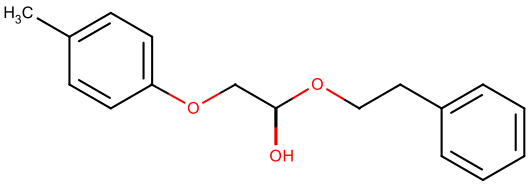
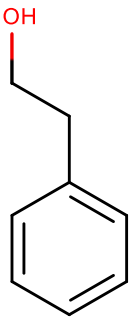
Appendix

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, 2018) 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 substance 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, 2018).
- 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	WoE Material
Principal Name	Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)-	Phenethyl alcohol
CAS No.	72987-59-8	60-12-8
Structure		
Similarity (Tanimoto Score)		0.35
SMILES	Cc1ccc(OCC(O)OCCc2ccccc2)cc1	OCCc1ccccc1
Endpoint		Genotoxicity
Molecular Formula	$C_{17}H_{20}O_3$	$C_8H_{10}O$
Molecular Weight (g/mol)	272.344	122.167
Melting Point (°C, EPI Suite)	128.89	−27.00
Boiling Point (°C, EPI Suite)	385.48	218.20
Vapor Pressure (Pa @ 25°C, EPI Suite)	6.00E-06	1.16E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.55E+02	2.22E+04
Log KOW	3.01	1.36
J_{max} (μg/cm^2/h, SAM)	0.78	355.17
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.17E-06	2.59E-02
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	H-acceptor-path3-H-acceptor	No alert found
Oncologic Classification	Not classified	Not classified
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 are insufficient toxicity data on Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- (CAS # 72987-59-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, phenethyl alcohol (CAS # 60-12-8) was identified as a WoE analog with sufficient data for toxicological evaluation.

Conclusions

- Phenethyl alcohol (CAS # 60-12-8) was used as a WoE analog for the target material ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)- (CAS # 72987-59-8) for the genotoxicity endpoint.
  - The target material and the WoE analog are structurally similar and belong to the alcohol group.
  - The key difference between the target material and the WoE analog is the position of the alcohol group, and that the target material has an additional benzene ring and two ether linkages that the WoE analog does not. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the WoE analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

- The physical–chemical properties of the target material and the WoE analog are sufficiently similar to enable a comparison of their toxicological properties.
- Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the WoE analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the material, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the WoE analog.
- The target material and the WoE analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the WoE analog and the target material.

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