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Short Review

RIFM fragrance ingredient safety assessment, ethyl benzoylacetate, CAS registry number 94-02-0

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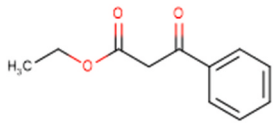

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Name: Ethyl benzoylacetate CAS Registry Number: 94-02-0

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., 2015, 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
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.

Ethyl benzoylacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl 3-hydroxy-3-phenylpropionate (CAS # 5764-85-2) show that ethyl benzoylacetate 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 benzoylacetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data show that there are no safety concerns for ethyl benzoylacetate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; ethyl benzoylacetate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; ethyl benzoylacetate 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, 2017b; RIFM, 2017a)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization. (Gerberick et al., 2005; RIFM, 1973)
Photoirritation/Photoallergenicity: Not photoirritating; not expected to be photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 2018)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 2.9 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 2.0 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 472.3 mg/L (RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 472.3 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.4723 □g/L
- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Ethyl benzoylacetate
2. **CAS Registry Number:** 94-02-0
3. **Synonyms:** Benzenepropanoic acid, .β.-oxo-, ethyl ester; Ethyl 3-phenyl-3-oxopropanoate; Ethyl 3-oxo-3-phenylpropanoate; Ethyl benzoylacetate
4. **Molecular Formula:** $C_{11}H_{12}O_3$
5. **Molecular Weight:** 192.21 g/mol
6. **RIFM Number:** 6090
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 284.38 °C (EPI Suite v4.11)
2. **Flash Point:** >200 °F; closed cup (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 1.71 (EPI Suite v4.11)
4. **Melting Point**: 55.82 °C (EPI Suite v4.11)
5. **Water Solubility:** 1212 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00275 mm Hg at 20 °C (EPI Suite v4.0), 0.001 mm Hg at 20 °C (FMA), 0.00446 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm under neutral and acidic conditions; molar absorption coefficients (156 and

256 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 at basic conditions, molar absorption coefficient (1361 L mol^{-1} • cm^{-1}) under basic conditions was above the benchmark.

9. **Appearance/Organoleptic:** A colorless oily liquid that turns yellowish upon storage or exposure to daylight and has a peculiar brandy-like odor of surprising tenacity.

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 v3.2.8)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.014% (RIFM, 2022)
2. **Inhalation Exposure*:** 0.000016 mg/kg/day or 0.0011 mg/day (RIFM, 2022)
3. **Total Systemic Exposure**:** 0.00056 mg/kg/day (RIFM, 2022)

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

Table 1
Summary of existing data on Ethyl benzoylacetate.

<table>
<tr><th rowspan="3">WoE Skin Sensitization Potency Category[1]</th><th colspan="4">Human Data</th><th colspan="3">Animal Data</th></tr>
<tr><th>NOEL-CNIH (induction) µg/cm²</th><th>NOEL-HMT (induction) µg/cm²</th><th>LOEL (induction) µg/cm²</th><th>WoE NESIL µg/cm²</th><th>LLNA[2] Weighted Mean EC3 Value µg/cm²</th><th>GPMT</th><th>Buehler</th></tr>
<tr><td rowspan="4">No evidence of sensitization[4]</td><td>1938</td><td>N/A</td><td>N/A</td><td>N/A</td><td>Negative up to 10000 (40%)</td><td>N/A</td><td>N/A</td></tr>
<tr><td colspan="4">In vitro Data[3]</td><td colspan="3">In silico protein binding alerts (OECD Toolbox v4.5)</td></tr>
<tr><td colspan="2">KE 1</td><td>KE 2</td><td>KE 3</td><td>Target Material</td><td>Autoxidation simulator</td><td>Metabolism simulator</td></tr>
<tr><td colspan="2">Borderline</td><td>Positive</td><td>Negative</td><td>Nucleophilic addition</td><td>No alert found</td><td>No alert found</td></tr>
</table>

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = 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]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

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

[4]Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

include these routes of exposure (Comiskey et al., 2015; Safford, 2015; Safford, 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 I, Low*

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

a. **Genotoxicity:** Ethyl 3-hydroxy-3-phenylpropionate (CAS # 5764-85-2)
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
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 benzoylacetate 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

Available (ECHA, 2022).

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 benzoylacetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic or clastogenic activity of ethyl benzoylacetate; however, read-across can be made to ethyl 3-hydroxy-3-phenylpropionate (CAS # 5764-85-2; see Section VI).

The mutagenic activity of ethyl 3-hydroxy-3-phenylpropionate 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 ethyl 3-hydroxy-3-phenylpropionate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. An increase (1.5-fold) in the mean number of revertant colonies was observed in strain WP2uvrA in the presence of an S9 activation system (RIFM, 2017b). However, the increase was within the 95% Historical Control Limit, not dose-responsive, and not reproducible, so it was considered not biologically relevant. Under the conditions of the study, ethyl 3-hydroxy-3-phenylpropionate was not mutagenic in the Ames test, and this can be extended to ethyl benzoylacetate.

The clastogenic activity of ethyl 3-hydroxy-3-phenylpropionate 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 ethyl 3-hydroxy-3-phenylpropionate in DMSO at concentrations up to 1940 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation. Ethyl 3-hydroxy-3-phenylpropionate did not induce binucleated cells with micronuclei when tested up to the cytotoxic or the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2017a). Under the conditions of the study, ethyl 3-hydroxy-3-phenylpropionate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to ethyl benzoylacetate.

Based on the data available, ethyl 3-hydroxy-3-phenylpropionate does not present a concern for genotoxic potential, and this can be extended to ethyl benzoylacetate.

Additional References: ECHA, 2022.

Literature Search and Risk Assessment Completed On: 01/27/23.

11.1.2. *Repeated dose toxicity*

There are insufficient repeated dose toxicity data on ethyl benzoylacetate or any read-across materials. The total systemic exposure to ethyl benzoylacetate 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 benzoylacetate or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to ethyl benzoylacetate (0.56 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/01/23.

11.1.3. *Reproductive toxicity*

There are insufficient reproductive toxicity data on ethyl benzoylacetate or any read-across materials. The total systemic exposure to ethyl benzoylacetate 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 benzoylacetate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to ethyl benzoylacetate (0.56 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/01/

23.

11.1.4. Skin sensitization

Based on the existing data, ethyl benzoylacetate presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, ethyl benzoylacetate is not considered a skin sensitizer. The data are summarized in Table 1. This material is predicted *in silico* (Roberts et al., 2007; OECD Toolbox v4.5). Ethyl benzoylacetate was found to be negative in the U-SENS tests, borderline in a direct peptide reactivity assay (DPRA), and positive in a KeratinoSens test (Natsch, 2013; Piroird et al., 2015). In a murine local lymph node assay (LLNA), ethyl benzoylacetate was found to be non-sensitizing when tested up to 40% (10000 μg/cm^2) (Gerberick et al., 2005). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 1938 μg/cm^2 ethyl benzoylacetate in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 40 volunteers (RIFM, 1973).

Based on the weight of evidence (WoE) from structural analysis, *in vitro* studies, and animal and human studies, ethyl benzoylacetate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/21/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra and *in vitro* study data, ethyl benzoylacetate would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, ethyl benzoylacetate is not expected to present a concern for photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm under the biologically relevant neutral condition, as well as the acidic condition. The corresponding molar absorption coefficients are below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Significant absorbance was observed under basic conditions, and the molar absorption coefficient (1361 L mol^{-1} • cm^{-1}) under that condition was above the benchmark of concern for photoirritation and photoallergy. However, for this assay, basic conditions are defined as pH 10 or greater and thus are not considered biologically relevant as the typical route of exposure is topical. In a 3T3-Neutral Red uptake photoirritation assay, ethyl benzoylacetate was not predicted to be photoirritating (RIFM, 2018). Based on the available UV/Vis absorption spectra and *in vitro* study data, ethyl benzoylacetate would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, ethyl benzoylacetate is not 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 indicate minor absorbance in the range of 290–700 nm under the biologically relevant neutral condition as well as the acidic condition. The molar absorption coefficients under neutral and acidic conditions were 156 and 256 L mol^{-1} • cm^{-1}, respectively, which are below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009). Under the basic condition, significant absorbance was observed, and the molar absorption coefficient (1361 L mol^{-1} • cm^{-1}) was above the benchmark.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/24/23.

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 benzoylacetate 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 benzoylacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.0011 mg/day. This exposure is 1273 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: 01/23/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl benzoylacetate 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 of 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 benzoylacetate 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 benzoylacetate 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 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, 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 $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current VoU (2019), ethyl benzoylacetate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation:

No data available.

Ecotoxicity:

No data available.

11.2.1.3. Other available data. Ethyl benzoylacetate 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	472.3			1000000	0.4723	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	1.7	1.7
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on available data, the RQ for this material is < 1. Additional assessment is not necessary.

The RIFM PNEC is 0.4723 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: 01/18/23.

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 Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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://pubchem.ncbi.nlm.nih.gov/source/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 08/01/23.

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.2023.114310.

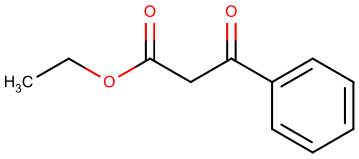
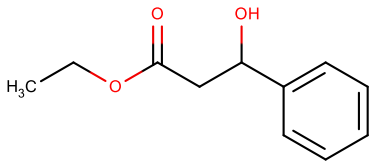
Appendix

Read-across Justification:

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with 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 Chemicals 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 the 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 the 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
Principal Name	Ethyl benzoylacetate	Ethyl 3-hydroxy-3-phenylpropionate
CAS No.	94-02-0	5764-85-2
Structure		
Similarity (Tanimoto Score)		0.65
SMILES	CCOC(=O)CC(=O)c1ccccc1	CCOC(=O)CC(O)c1ccccc1
Endpoint		Genotoxicity
Molecular Formula	$C_{11}H_{12}O_3$	$C_{11}H_{14}O_3$
Molecular Weight (g/mol)	192.214	194.23
Melting Point (°C, EPI Suite)	55.82	57.61
Boiling Point (°C, EPI Suite)	284.38	297.55
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.44E-02	1.05E-02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.21E+03	7.55E+03
Log KOW	1.87	1.52
J_{max} (μg/cm^2/h, SAM)	7.32	23.80
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.14E-03	9.24E-05
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.5)	No alert found	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	H-acceptor-path3-H-acceptor
Oncologic Classification	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

Summary

There are insufficient toxicity data on ethyl benzoylacetate (CAS # 94-02-0). 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, ethyl 3-hydroxy-3-phenylpropionate (CAS # 5764-85-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Ethyl 3-hydroxy-3-phenylpropionate (CAS # 5764-85-2) was used as a read-across analog for the target material, ethyl benzoylacetate (CAS # 94-02-0), for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the aromatic ester group.
  - The key difference between the target material and the read-across analog is the target material has a ketone while the read-across analog has a secondary alcohol in the same position. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across 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 read-across analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, 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 v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across have H-acceptor alerts for *in vivo* mutagenicity, but only the read-across has a Michael addition to quinone and quinone-like structures alert. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. The data on the read-across analog confirms that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts and predictions are superseded by the data.
  - The target material and the read-across 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 read-across analog and the target material.

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