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Short Review

RIFM fragrance ingredient safety assessment, benzoic acid, 2-hydroxy-5--methyl-, methyl ester, CAS Registry Number 22717-57-3

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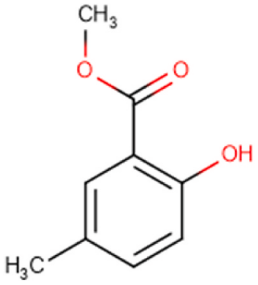
Name: Benzoic acid, 2-hydroxy-5-methyl-, methyl ester CAS Registry Number: 22717-57-3



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)
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; 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 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

(*continued on next column*)

(*continued*)

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.

Benzoic acid, 2-hydroxy-5-methyl-, methyl ester was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs methyl 2,4-dihydroxy-*m*-toluate (CAS # 33662-58-7) and methyl atrarate (CAS # 4707-47-5) show that benzoic acid, 2-hydroxy-5-methyl-, methyl ester 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 benzoic acid, 2-hydroxy-5-methyl-, methyl ester 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 benzoic acid, 2-hydroxy-5-methyl-, methyl ester for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; benzoic acid, 2-hydroxy-5-methyl-, methyl ester is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; benzoic acid, 2-hydroxy-5-methyl-, methyl ester was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2009; RIFM, 2000a; RIFM, 2000b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: No concern for skin sensitization. (RIFM, 2022; RIFM, 2021)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 2.95 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 55.71 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 22.39 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: 22.39 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.02239 μg/L
- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Benzoic acid, 2-hydroxy-5-methyl-, methyl ester
2. **CAS Registry Number:** 22717-57-3
3. **Synonyms:** methyl 6-hydroxy-*m*-toluate; Methyl 2-hydroxy-5-methylbenzoate; Benzoic acid, 2-hydroxy-5-methyl-, methyl ester
4. **Molecular Formula:** $C_9H_{10}O_3$
5. **Molecular Weight:** 166.17 g/mol
6. **RIFM Number:** 6436
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 269.1 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.15 (EPI Suite)
4. **Melting Point**: 65.99 °C (EPI Suite)
5. **Water Solubility:** 496.5 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00962 mm Hg at 20 °C (EPI Suite v4.0), 0.0157 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficients (216, 220, and 196 L mol^{-1} • cm^{-1} for neutral, acidic, and basic conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.045% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0000057 mg/kg/day or 0.00041 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00054 mg/kg/day (RIFM, 2019)

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
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2. **Analogs Selected**:
   a. **Genotoxicity:** Methyl 2,4-dihydroxy-*m*-toluate (CAS # 33662-58-7) and methyl atrarate (CAS # 4707-47-5)
   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
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

Benzoic acid, 2-hydroxy-5-methyl-, methyl ester is not reported to occur in foods by the VCF*.

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

9. REACH dossier

Benzoic acid, 2-hydroxy-5-methyl-, methyl ester has been pre-registered for 2010; no dossier available as of 12/01/22.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, benzoic acid, 2-hydroxy-5-methyl-, methyl ester does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Benzoic acid, 2-hydroxy-5-methyl-, methyl ester was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays 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 activity of benzoic acid, 2-hydroxy-5-methyl-, methyl ester; however, read-across can be made to methyl 2,4-dihydroxy-*m*-toluate (CAS # 33662-58-7; see Section VI).

The mutagenic activity of methyl 2,4-dihydroxy-*m*-toluate 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 TA102 were treated with methyl 2,4-dihydroxy-*m*-toluate 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, 2009). Under the conditions of the study, methyl 2,4-dihydroxy-*m*-toluate was not mutagenic in the Ames test, and this can be extended to benzoic acid, 2-hydroxy-5-methyl-, methyl ester.

There are no studies assessing the clastogenic activity of benzoic acid, 2-hydroxy-5-methyl-, methyl ester; however, read-across can be made to methyl atrarate (CAS # 4707-47-5; see Section VI).

The clastogenicity of methyl atrarate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovary cells were treated with methyl atrarate in acetone at concentrations up to 5000 μg/mL in the presence and absence of metabolic activation. Statistically significant increases in the frequency of cells with structural

chromosomal aberrations or polyploid cells were observed at 100 and 120 μg/mL in the 4-h treatment with and without S9 metabolic activation and 150 μg/mL in the 4-h treatment without S9 metabolic activation (RIFM, 2000a). The Cochran-Armitage test was also positive for a dose-response. Under the conditions of the study, methyl atrarate was considered to be clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to benzoic acid, 2-hydroxy-5-methyl-, methyl ester.

To further evaluate the clastogenic potential of methyl atrarate, the clastogenic activity of methyl atrarate was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via intraperitoneal injection to groups of male and female ICR mice. Doses of 95, 190, or 380 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow in female mice at 48 h after treatment with 380 mg/kg (RIFM, 2000b). However, this increase was not considered biologically significant. In female mice tested at 380 mg/kg in the 48-h harvest time, the mean polychromatic erythrocytes (PCEs)/total erythrocytes ratio was 0.532 ± 0.04, and the ratio of total micronuclei per PCE scored was 11/10000 PCE. The breakdown per animal for the total micronuclei per PCE scored was 1/2000 PCE, 2/2000 PCE, 3/2000 PCE, 2/2000 PCE, and 3/2000 PCE in the 5 female mice. The historical control range for the solvent-control females for the ratio of PCEs/total erythrocytes was 0.23–0.92, and the total number of micronuclei per 1000 PCEs scored was 0–7. Each female was within these ranges, and therefore, the increase was not considered biologically relevant. Under the conditions of the study, methyl atrarate was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to benzoic acid, 2-hydroxy-5-methyl-, methyl ester.

Based on the data available, methyl 2,4-dihydroxy-*m*-toluate or methyl atrarate does not present a concern for genotoxic potential, and this can be extended to benzoic acid, 2-hydroxy-5-methyl-, methyl ester.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/25/23.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on benzoic acid, 2-hydroxy-5-methyl-, methyl ester or any read-across materials. The total systemic exposure to benzoic acid, 2-hydroxy-5-methyl-, methyl ester 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 benzoic acid, 2-hydroxy-5-methyl-, methyl ester or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to benzoic acid, 2-hydroxy-5-methyl-, methyl ester (0.54 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: 10/25/23.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on benzoic acid, 2-hydroxy-5-methyl-, methyl ester or any read-across materials. The total systemic exposure to benzoic acid, 2-hydroxy-5-methyl-, methyl ester 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 benzoic acid, 2-hydroxy-5-methyl-, methyl ester or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to benzoic acid, 2-hydroxy-5-methyl-, methyl ester (0.54 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: 10/25/23.

11.1.4. Skin sensitization

Based on the existing data, benzoic acid, 2-hydroxy-5-methyl-, methyl ester presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, benzoic acid, 2-hydroxy-5-methyl-, methyl ester is not considered a skin sensitizer. The data are summarized in 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). Benzoic acid, 2-hydroxy-5-methyl-, methyl ester was predicted not to be sensitizing in an *in vitro* KeratinoSens and human cell line activation test (h-CLAT) (RIFM, 2022; RIFM, 2021).

Based on the weight of evidence (WoE) from structural analysis and *in vitro* studies, benzoic acid, 2-hydroxy-5-methyl-, methyl ester does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/25/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, benzoic acid, 2-hydroxy-5-methyl-, methyl ester would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for benzoic acid, 2-hydroxy-5-methyl-, methyl ester in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, benzoic acid, 2-hydroxy-5-methyl-, methyl ester does not present a concern for photoirritation or 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. The molar absorption coefficients (216, 220, and 196 L mol^{-1} • cm^{-1} for neutral, acidic, and basic conditions, respectively) are below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/25/23.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for benzoic acid, 2-hydroxy-5-methyl-, methyl ester 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 benzoic acid, 2-hydroxy-5-methyl-, methyl ester. Based on the Creme RIFM Model, the inhalation exposure is 0.00041 mg/day. This exposure is 3415 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: 10/26/23.

Table 1
Summary of existing data on benzoic acid, 2-hydroxy-5-methyl-, methyl ester.

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 Weighted Mean EC3 Value µg/cm²	GPMT[4]	Buehler[4]
No evidence of sensitization[6]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	In Vitro Data[5]				*In Silico* Protein Binding Alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	N/A	Negative	Negative		No alert found	No alert found	Michael addition

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; 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]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Studies conducted according to the OECD TG 406 are included in the table.
[5]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.
[6]Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of benzoic acid, 2-hydroxy-5-methyl-, methyl ester was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA 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, benzoic acid, 2-hydroxy-5-methyl-, methyl ester 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 benzoic acid, 2-hydroxy-5-methyl-, methyl ester as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2019), benzoic acid, 2-hydroxy-5-methyl-, methyl ester does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. ***Biodegradation***:

No data available.

Ecotoxicity:

RIFM, 2001: A *Daphnia magna* immobilization test was conducted according to the OECD 202 (Part I) method under static conditions. The 48-h EC50 was reported to be 11.1 mg/L.

11.2.1.3. Other available data. Benzoic acid, 2-hydroxy-5-methyl-, methyl ester has been pre-registered for REACH with no additional data at this time.

11.2.2. Risk assessment refinement

Since benzoic acid, 2-hydroxy-5-methyl-, methyl ester has passed the screening criteria; measured data is included for completeness only and has not been used in PNEC derivation.

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

Literature Search and Risk Assessment Completed On: 10/25/23.

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

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>22.39 mg/L</u>			1000000	0.02239 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.15	3.15
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 0.02239 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

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 11/09/23.

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.2023.114370.

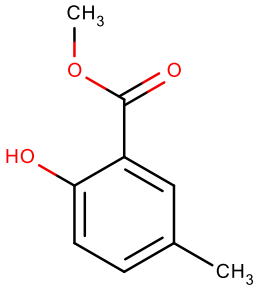
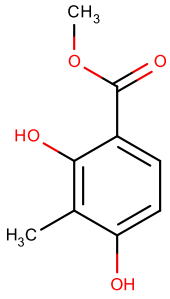
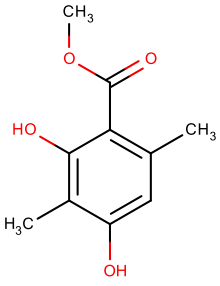
Appendix

Read-across Justification

Methods

The read-across analogs were 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 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, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2018).
- 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, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2018).
- 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	Benzoic acid, 2-hydroxy-5-methyl-, methyl ester	Methyl 2,4-dihydroxy-*m*-toluate	Methyl atrarate
CAS No.	22717-57-3	33662-58-7	4707-47-5
Structure			
Similarity (Tanimoto Score)		0.56	0.42
Endpoint		Genotoxicity	Genotoxicity
Molecular Formula	$C_9H_{10}O_3$	$C_9H_{10}O_4$	$C_{10}H_{12}O_4$
Molecular Weight (g/mol)	166.18	182.18	196.20
Melting Point (°C, EPI Suite)	−1.00	108.17	119.94
Boiling Point (°C, EPI Suite)	244.50	314.50	327.81
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.09	0.00	0.00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	496.50	1070.00	310.60
Log K_{OW}	3.15	2.67	3.22
J_{max} (μg/cm^2/h, SAM)	37.07	30.29	13.95
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.51	0.00	0.00
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)	Michael addition|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals ≫ Alkyl phenols	Michael addition|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals ≫ Alkyl phenols	Michael addition|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals ≫ Alkyl phenols
Carcinogenicity (ISS)	No alert found	No alert found	No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
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)**	H-acceptor-path3-H-acceptor	H-acceptor-path3-H-acceptor	H-acceptor-path3-H-acceptor
Oncologic Classification	Phenol-type Compounds	Phenol-type Compounds	Phenol-type Compounds
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 benzoic acid, 2-hydroxy-5-methyl-, methyl ester (CAS # 22717-57-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, methyl 2,4-dihydroxy-*m*-toluate (CAS # 33662-58-7) and methyl atrarate (CAS # 4707-47-5) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Methyl 2,4-dihydroxy-*m*-toluate (CAS # 33662-58-7) is used as a read-across analog for benzoic acid, 2-hydroxy-5-methyl-, methyl ester (CAS # 22717-57-3) for the genotoxicity endpoint.
  - o The target and the read-across belong to a class of aromatic esters.
    - ○The key difference between the target and the read-across is that the target has a hydroxy group and methyl group at the 2nd and 5th positions, respectively, whereas the read-across analog has a hydroxy group at the 2nd and 4th positions and a methyl group at the 3rd position, respectively. These structural differences are 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.
    - ○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 read-across have a DNA binding alert for Michael addition by OECD QSAR Toolbox v4.5. This alert is due to the fact that the hydroxy group in both target material and read-across material has a methyl substituent either at the ortho position or at the para position. As a result, quinone methide formation is possible in both target material and read-across material. As described in the genotoxicity section above, based on the current existing data and the use levels, the read-across analog does not pose a concern for genetic toxicity. Data superseded predictions in this case.
    - ○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.
- Methyl atrarate (CAS # 4707-47-5) is used as a read-across analog for benzoic acid, 2-hydroxy-5-methyl-, methyl ester (CAS # 22717-57-3) for the genotoxicity endpoint.
    - ○The target and the read-across belong to a class of aromatic esters.
    - ○The key difference between the target and the read-across is that the target has a hydroxy group and methyl group at the 2nd and 5th positions, respectively, whereas the read-across analog has a hydroxy group at the 2nd and 4th positions and a methyl group at the 3rd and 6th positions, respectively. These structural differences are 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.
    - ○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 read-across analog have a DNA binding alert for Michael addition by OECD QSAR Toolbox v4.5. This alert is due to the fact that the hydroxy group in both the target material and read-across material has a methyl substituent either at the ortho position or at the para position. As a result, quinone methide formation is possible in both the target material and read-across material. As described in the genotoxicity section above, based on the current existing data and the use levels, the read-across analog does not pose a concern for genetic toxicity. Data superseded predictions in this case.
    - ○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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