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RIFM fragrance ingredient safety assessment, eugenyl acetate, CAS Registry Number 93-28-7

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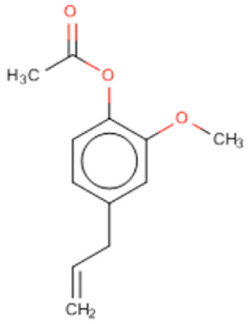
Version: 121018. This version replaces any previous versions.

Name: Eugenol acetate
CAS Registry Number: 93-28-7



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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
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
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union

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GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable 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
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Eugenyl acetate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and the read-across analog isoeugenol acetate (CAS # 93-29-8) show that eugenyl acetate is not expected to be genotoxic. Data on eugenyl acetate provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on read-across analogs isoeugenol (CAS # 97-54-1) and acetic acid (CAS # 64-19-7) provide a calculated MOE >100 for the developmental and reproductive toxicity endpoint. Data show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; eugenyl acetate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; eugenyl acetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: Eugenyl acetate; ECHA, 2017; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day.	Hagan et al., (1967)
Developmental and Reproductive Toxicity: Developmental toxicity: NOAEL = 250 mg/kg/day. Reproductive toxicity: NOAEL = 230 mg/kg/day.	(NTP, 1999; NTP, 2002)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	RIFM, (2005)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 81% (OECD 301F)	RIFM, (2011)
Bioaccumulation: Screening-level: 48.81 L/kg	(EPI Suite; US EPA, 2012a)
Ecotoxicity: Screening-level: LC50: 152.5 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: LC50: 152.5 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.152 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; Cleared at Screening-level

1. Identification

1. **Chemical Name:** Eugenyl acetate
2. **CAS Registry Number:** 93-28-7
3. **Synonyms:** Acetyl eugenol; 4-Allyl-2-methoxyphenyl acetate; Eugenol acetate; 2-Methoxy-4-(2-propen-1-yl)phenyl acetate; Phenol, 2-methoxy-4-(2-propenyl)-, acetate; アルカン酸（C = 1 ~ 2）オイゲニル; Eugenyl acetate
4. **Molecular Formula:** $C_{12}H_{14}O_3$
5. **Molecular Weight:** 206.24
6. **RIFM Number:** 297
7. **Stereochemistry:** Isomer not specified. No isomeric center and no isomers possible.

2. Physical data

1. **Boiling Point:** 282 °C (FMA Database), 284.53 °C (EPI Suite)
2. **Flash Point:** >93 °C (GHS), >200 °F; CC (FMA Database)
3. **Log K_{OW}:** log P_{ow} = 2.3 (RIFM, 2013b), 3.06 (EPI Suite)
4. **Melting Point**: 25 °C (FMA Database), 59.29 °C (EPI Suite)
5. **Water Solubility:** 98.28 mg/L (EPI Suite)
6. **Specific Gravity:** 1.080 (FMA Database)
7. **Vapor Pressure:** 0.00265 mm Hg @ 20 °C (EPI Suite v4.0), 0.006 mm Hg 20 °C (FMA Database), 0.00475 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra**: Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** White granular crystals with a mild, sweet-spicy, balsamic-fruity odor reminiscent of carnation and clove oil

(*continued on next page*)

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.023% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.000063 mg/kg/day or 0.0048 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00091 mg/kg/day (RIFM, 2018)

*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; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in section 5. 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; and Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%

Jimbo (1983): Lower human abdominal skin was used to determine the dermal absorption of eugenyl acetate following the removal of subcutaneous tissue. In a modified Baumberger's method, the epidermis was fixed to a glass tube placed inside 1 arm of a U-shaped glass chamber followed by addition of 5 mL saline to the chamber such that the solution was in contact with the bottom of the epidermis. A 0.2 mL aliquot of test material was applied to the top of the epidermis, and glass tube was sealed with parafilm to avoid evaporation. The chamber was maintained at 21 °C and 55% relative humidity for 72 h. The compound was extracted in ether, dehydrated, filtered, and condensed. A 2-μL aliquot of the condensed sample was analyzed via GC-MS; the experiments were repeated 6 times. Percent penetration was determined to be 0.092% ± 0.017%. Since the study does not report the amount of recovered material, conservative dermal absorption is considered to be 100% for this safety assessment.

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
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2. Analogs Selected:
a. **Genotoxicity:** Isoeugenol acetate (CAS # 93-29-8)
b. **Repeated Dose Toxicity:** None
c. **Developmental and Reproductive Toxicity:** Isoeugenol (CAS # 97-54-1); acetic acid (CAS # 64-19-7)
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix

7. Metabolism

Castro et al., 2004: Eugenyl acetate is an ester of eugenol that undergoes rapid and complete hydrolysis ultimately following the existing toxicity profile of eugenol. Castro et al. (2004) compared the rate of hydrolysis of eugenyl acetate by hepatic microsomes obtained from male SD rat and human livers. When 500 μM eugenyl acetate was incubated with 0.0125 mg/mL microsomal protein and appropriate cofactors, the ester was hydrolyzed completely to eugenol within 15 min. The kinetic analysis of this hydrolytic reaction in hepatic microsomes (4.8–970 μM, 3.0 min incubation) yielded the following kinetic values: reaction in hepatic microsomes (4.8–970 μM, 3.0 min incubation) yielded the following kinetic values:

Species	V_{max} (nmol/min/mg of protein)	K_m (μM)
Rat	3829	97
Human – males	3656	72
Human – females	2748	52

These results demonstrate that rat plasma preparations readily hydrolyze eugenyl acetate as observed in human liver, plasma, and skin enzymes. This further minimizes systemic exposure of the treatment material when used under appropriate conditions.

8. Natural occurrence (discrete chemical) or Composition (NCS)

Eugenyl acetate is reported to occur in the following foods by the VCF*:

Alpinia species	Mentha oils
Cinnamomum species	Ocimum species
Cloves (*Eugenia caryophyllata Thunberg*)	Piper Betle L. Cultivars
Laurel (*Laurus nobilis L.*)	Rooibos tea (*Aspalathus linearis*)

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

9. Reach dossier

Available; accessed 10/03/18.

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 and use levels, eugenyl acetate does not present a concern for genotoxic potential.

11.1.1.1. Risk assessment. Eugenyl acetate 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, 2013a). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional

assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of eugenyl acetate 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/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* strain WP2uvrA were treated with eugenyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. The test material caused a visible reduction in the growth of the bacterial background lawns at 1500 μg/plate in strains TA1535, TA98, and TA1537 and at 5000 μg/plate in the strain TA100. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2017). Under the conditions of the study, eugenyl acetate was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of eugenyl acetate; however, read-across can be made to isoeugenol acetate (CAS # 93-29-8; see Section 6). The clastogenic activity of isoeugenol acetate 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 isoeugenol acetate in DMSO at concentrations up to 2060 μg/mL in a dose range finding (DRF) study. Micronuclei analysis was done at 400 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Isoeugenol acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, isoeugenol acetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to eugenyl acetate.

Based on the available data, isoeugenol acetate does not present a concern for genotoxic potential, and this can be applied to eugenyl acetate.

Additional References: RIFM, 2003a.

Literature Search and Risk Assessment Completed On: 11/18/18.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for eugenyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There is sufficient data on eugenyl acetate to support the repeated dose toxicity endpoint. A 19-week chronic dietary toxicity study was conducted in weanling Osborne-Mendel rats. Groups of 10 rats/sex/dose were fed diet containing test material, eugenyl acetate, at dose levels of 0, 1000, 2500, or 10000 ppm (equivalent to 0, 50, 125, or 500 mg/kg/day, following the conversion factors for old rats, available in the JECFA guidelines for Food Additives). No treatment-related changes were reported on growth, hematological parameters, and histopathology at any dose levels. The NOAEL for repeated dose toxicity was considered to be 10000 ppm or 500 mg/kg/day, the highest dose tested (Hagan et al., 1967; data also available in Bar and Griepentrog, 1967). **Therefore, the eugenyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the eugenyl acetate NOAEL in mg/kg/day by the total systemic exposure to eugenyl acetate, 500/0.00091 or 549451.**

In addition, the total systemic exposure to eugenyl acetate (0.91 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: 11/20/18.

11.1.3. Developmental and reproductive toxicity

The MOE for eugenyl acetate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on eugenyl acetate. Eugenyl acetate is expected to hydrolyze to eugenol and acetic acid (CAS # 64-19-7; see Section 6). Based on the available data on acetic acid, acetic acid does not show specific developmental and reproductive toxicity. Thus, acetic acid does not pose any systemic (repeated dose) or developmental or reproductive toxicity to human health when used in fragrances.

Read-across material isoeugenol (CAS # 97-54-1; see Section 6), an isomer of eugenol has sufficient developmental and reproductive toxicity data. In a GLP-compliant NTP developmental toxicity study, isoeugenol was administered via oral gavage at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil to pregnant female Sprague Dawley rats (25 dams/group) on gestation days (GDs) 6–19. High incidences of aversion to treatment (i.e., rooting behavior) was noted in all treatment group dams. A dose-related statistically significant decrease in maternal bodyweight gain and gestational weight gain was reported at all dose levels. A statistically significant decrease in food consumption was reported at 1000 mg/kg/day. The gravid uterine weight was significantly decreased among 500 and 1000 mg/kg/day dose group dams. A statistically significant decrease in body weight and a statistically significant increase in the incidence of non-ossified sternebrae were reported in 1000 mg/kg/day dose group pups. The NOAEL for developmental toxicity was considered to be 250 mg/kg/day, based on decreased pup body weight and increased incidences of non-ossified sternebrae among high-dose group pups and decreased gravid uterine weight among mid- and high-dose group dams (NTP, 1999; George et al., 2001).

In a GLP-compliant NTP multigenerational continuous breeding study, isoeugenol was administered via oral gavage to Sprague Dawley rats (20 animals/sex/group) (F0) at doses of 0, 70, 230, or 700 mg/kg/day in corn oil from 1 week prior to mating to study day 179. One of 3 litters (F1) from each dose group was dosed starting on postnatal day (PND) 21 until necropsy on PND 186. This litter was assigned to mating at approximately PND 80 and produced F2 litters. Mortality in F0 was as follows: 2 males at 70 mg/kg/day; 1 male and 2 females at 230 mg/kg/day; 1 male and 8 females at 700 mg/kg/day. Under the conditions of this study, isoeugenol produced evidence of non-reproductive toxicity at all dose levels as reported by the presence of hyperkeratosis and hyperplasia in the non-glandular stomachs and decreased body weights of F0 and F1 animals (230 mg/kg/day males and 700 mg/kg/day, both sexes). Sperm parameters and vaginal cytology were unaffected in the F0 and F1 generations. A statistically significant decrease in live male pups of the F1 generation and a statistically significant decrease in F1 pup weight were seen at 700 mg/kg/day. In order to determine whether fertility effects were due to males or females, a separate study of outbred F0 animals was conducted. Pups from these F0 animals showed a decrease in live male pups that was potentially due to reproductive toxicity in females. Gross necropsy showed no significant alterations of the organs. Therefore, the NOAEL for reproductive was considered to be 230 mg/kg/day, based on a decreased number of male pups per litter during the F0 cohabitation and decreased male and female pup weights during the F1 cohabitation among high-dose group animals (NTP, 2002; Layton et al., 2001).

Based on the toxic effects reported in the reproductive toxicity studies, a NOAEL of 230 mg/kg/day was selected from the multigeneration study for the reproductive toxicity endpoint, and a NOAEL of 250 mg/kg/day was selected for the developmental toxicity endpoint.

The eugenyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the isoeugenol NOAEL in mg/kg/day by the total systemic exposure to eugenyl acetate, 250/0.00091 or 274725.

The eugenyl acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the isoeugenol NOAEL in mg/kg/day by the

total systemic exposure to eugenyl acetate, 230/0.00091 or 252747.

In addition, the total systemic exposure to eugenyl acetate (0.91 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/19/18.

11.1.4. Skin sensitization

Based on the existing data, eugenyl acetate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, eugenyl acetate does not present a concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0). However, in a murine local lymph node assay (LLNA), eugenyl acetate was not sensitizing up to the highest tested concentration of 50% (12500 μg/cm^2) (RIFM, 2005). In guinea pigs, open and closed epicutaneous tests did not present reactions indicative of sensitization (Klecak, 1985; Ishihara et al., 1986; Itoh, 1982). In a human maximization test, no skin sensitization reactions were observed when eugenyl acetate was tested at 20% in 25 subjects (RIFM, 1972). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 9448 μg/cm^2 (8%) of eugenyl acetate in diethyl phthalate/ethanol 3:1, no reactions indicative of sensitization was observed in any of the 105 volunteers (RIFM, 2003b).

Based on weight of evidence from structural analysis and animal and human studies, eugenyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 2002; ECHA, 2017; FCT, 1974.

Literature Search and Risk Assessment Completed On: 11/15/18.

11.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, eugenyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. The available UV/Vis spectra for eugenyl acetate indicate minor absorbance between 290 and 700 nm. The molar absorption coefficient for wavelengths between 290 and 700 nm is below the benchmark (1000 L mol^{-1} · cm^{-1}) considered not to be of concern for phototoxic effects (Henry et al., 2009). Based on UV/Vis absorption spectra, eugenyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.6. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) for eugenyl acetate were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/11/18.

11.1.7. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for eugenyl acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.7.1. Risk assessment. There are no inhalation data available on eugenyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.0048 mg/day. This exposure is 292 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: 04/23/18.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of eugenyl acetate 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, eugenyl acetate 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 eugenyl acetate 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 $\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). 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 current VoU (IFRA, 2015), eugenyl acetate does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. RIFM, 2011**:** The ready biodegradability of the test material was evaluated using the Manometric Respirometry Test following the OECD 301F method. Under the conditions of the study, biodegradation of 81% was observed after 28 days.

Ecotoxicity: No data available.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	152.5			1,000,000	0.152	

11.2.4. Other available data

Eugenyl acetate has been registered for REACH with no additional data is available at this time.

11.2.5. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} used	2.3	2.3
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.152 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 volumes of use.

Literature Search and Risk Assessment Completed On: 11/06/18.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 05/20/19.

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.2020.111630.

Appendix

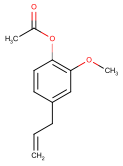
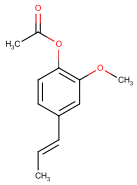
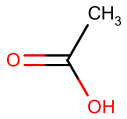
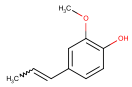
Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also 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, 2016).

- 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization 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 and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Eugenyl acetate	Isoeugenyl acetate	Acetic acid	Isoeugenol
CAS No.	93-28-7	93-29-8	64-19-7	97-54-1
Structure				
Similarity (Tanimoto Score)		0.69	0.08	0.45
Read-across Endpoint		• Genotoxicity	• Developmental and reproductive toxicity	• Developmental and reproductive toxicity
Molecular Formula	$C_{12}H_{14}O_3$	$C_{12}H_{14}O_3$	$C_2H_4O_2$	$C_{10}H_{12}O_2$
Molecular Weight	206.24	206.24	60.05	164.20
Melting Point (°C, EPI Suite)	59.29	59.35	16.64	33.50
Boiling Point (°C, EPI Suite)	284.53	290.44	117.90	266.00
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.634	0.207	2.09E+003	1.80
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.06	2.99	−0.17	3.04
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	98.28	114.70	1e+006	810.00
J_{max} (μg/cm^2/h, SAM)	7.29	4.99	6283.04	79.64
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.63E-001	3.12E-001	1.45E-002	2.70E-003
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ S	• AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ S		
DNA Binding (OECD QSAR Toolbox v4.2)	• SN1|SN1 ≫ Carbenium Ion Formation|SN1 ≫ Carbenium Ion Formation ≫ Allyl benzenes	• No alert found		
Carcinogenicity (ISS)	• Carcinogen (good reliability)	• Non-Carcinogen (low reliability)		
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found		
In Vitro Mutagenicity (Ames, ISS)	• Alkenylbenzenes	• No alert found		
In Vivo Mutagenicity (Micronucleus, ISS)	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor		
Oncologic Classification	• Not classified	• Not classified		
Reproductive and Developmental Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group		• Non-binder, non-cyclic structure	• Weak binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (low reliability)		• Toxicant (low reliability)	• Non-Toxicant (low reliability)
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• Can not be metabolized further	• See Supplemental Data 3

Summary

There are insufficient toxicity data on eugenyl acetate (CAS # 93-28-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, isoeugenyl acetate

(CAS # 93-29-8), acetic acid (CAS # 64-19-7), and isoeugenol (CAS # 97-54-1) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target substance eugenyl acetate (CAS # 93-28-7) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to and eugenol (CAS # 97-53-0) and acetic acid (CAS # 64-19-7) in the first step with 0.95 probability. Hence, isoeugenol (CAS # 97-54-1) is a structural isomer of eugenol (CAS # 97-53-0) with only a difference of vinylene and a vinyl bond. They have similar reactivity and toxicity for reproductive and developmental toxicity. Therefore, isoeugenol (CAS # 97-54-1) and acetic acid (CAS # 64-19-7) can be used as read-across analogs for the target material. The read-across analogs were in domain for the *in vivo* rat and in domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden and a justification is provided.

Conclusions

- Isoeugenyl acetate (CAS # 93-29-8) was used as a read-across analog for the target material eugenyl acetate (CAS # 93-28-7) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to a class of substituted phenylpropenyl esters.
  - o The target substance and the read-across analog share a phenol ring moiety substituted with an ortho acetylphenol and a para propenyl group.
  - o The key difference between the target substance and the read-across analog is the position of the double bond in the propenyl substituent. The target material has the double bond at C-2, whereas the read-across analog has the substituent at C-1. The read-across analog can form a quinone methide upon metabolic oxidation and is therefore more reactive than the target. This structural difference is appropriate for evaluating the genotoxicity endpoint.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog have alerts for forming Schiff bases and undergoing S_N1 nucleophilic addition reactions. This is due to the fact that both substances bear allyl benzenes, and they are acetate esters. Allyl benzenes have been suggested to be metabolized in reactive carbenium ions via initial hydroxylation followed by sulfation. The carbenium ion can then alkylate DNA via an S_N1 mechanism. The data described in the genetic toxicity section confirm that the read-across analog does not pose a concern for genetic toxicity. The predictions are superseded by data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Read-across alcohol isoeugenol (CAS # 97-54-1) and read-across acid acetic acid (CAS # 64-19-7) are used as read-across analogs for the target ester eugenyl acetate (CAS # 93-28-7) for the reproductive and developmental toxicity endpoints.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - o Structural differences between the target substance and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o The target substance and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target substance and the read-across analog.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target substance.

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