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RIFM fragrance ingredient safety assessment, 4-ethylguaiacol, CAS Registry Number 2785-89-9

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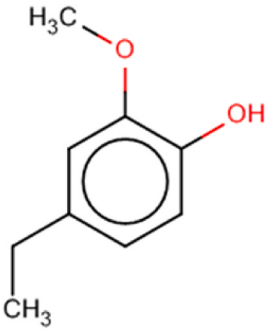
Name: 4-Ethylguaiacol CAS Registry Number: 2785-89-9



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, 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
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 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).

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(*continued*)

*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.

4-Ethylguaiacol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog guaiacol (CAS # 90-05-1) show that 4-ethylguaiacol is not expected to be genotoxic. Data from analog eugenol (CAS # 97-53-0) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure to 4-ethylguaiacol is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from analog 2-methoxy-4-propylphenol (CAS # 2785-87-7) provided 4-ethylguaiacol a No Expected Sensitization Induction Level (NESIL) of 1700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 4-ethylguaiacol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4-ethylguaiacol 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. (Pool and Lin, 1982; Haworth et al., 1983; ECHA REACH Dossier: Guaiacol; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 300 mg/kg/day. NTP (1983)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 1700 μg/cm^2. (RIFM, 2015; RIFM, 1998)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/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: 2.8 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 17.17 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 101.8 mg/L (RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA ENV Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: LC50: 101.8 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.1018 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 4-Ethylguaiacol
2. **CAS Registry Number:** 2785-89-9
3. **Synonyms:** 4-Ethyl-2-methoxyphenol; Homocreosol; 1-Hydroxy-2-methoxy-4-ethylbenzene; 2-Methoxy-4-ethylphenol; Phenol, 4-ethyl-2-methoxy-; 4-Ethylguaiacol
4. **Molecular Formula:** $C_9H_{12}O_2$
5. **Molecular Weight:** 152.19 g/mol
6. **RIFM Number:** 6200
7. **Stereochemistry:** Isomer not specified. No isomeric center and no isomers possible.

2. Physical data

1. **Boiling Point:** 234 °C (Fragrance Materials Association [FMA] Database), 248.39 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.35 (Smith et al., 2002), 2.38 (EPI Suite)
4. **Melting Point**: 11 °C (FMA Database), 51.22 °C (EPI Suite)
5. **Water Solubility:** 693.8 mg/L (EPI Suite)
6. **Specific Gravity:** 1.060 (FMA Database)
7. **Vapor Pressure:** 0.0154 mm Hg at 20 °C (EPI Suite v4.0), 0.003 mm Hg at 20 °C (FMA Database), 0.0248 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance in the region 290–700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} •cm^{-1}).
9. **Appearance/Organoleptic:** An almost colorless, oily liquid with a warm, sweet-and-spicy-medicinal, very powerful odor reminiscent of guaiacol and eugenol at the same time; the odor is extremely diffusive and penetrating

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00015% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.0000005 mg/kg/day or 0.000034 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.000012 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford, 2015, 2017; and 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, 2015, 2017; and 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 v4.2
I	I	I

6.2. Analogs Selected

a. **Genotoxicity:** Guaiacol (CAS # 90-05-1)
b. **Repeated Dose Toxicity:** Eugenol (97-53-0); Weight of evidence (WoE) 2-Ethoxy-4-methylphenol (CAS # 2563-07-7)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 2-Methoxy-4-propylphenol (CAS # 2785-87-7)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

8. Natural occurrence

4-Ethylguaiacol is reported to occur in the following foods by the VCF*:

Beer.
Wine.
Whisky.
Sherry.
Coffee.
Fish.
Cider (apple wine).
Vinegar.
Salami.
Rum.

*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

4-Ethylguaiacol has been pre-registered for 2010; no dossier available as of 10/06/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 4-ethylguaiacol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.13
2	Products applied to the axillae	0.039
3	Products applied to the face/body using fingertips	0.78
4	Products related to fine fragrances	0.73
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.18
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.18
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.18
5D	Baby cream, oil, talc	0.060
6	Products with oral and lip exposure	0.43
7	Products applied to the hair with some hand contact	1.5
8	Products with significant ano-genital exposure (tampon)	0.060

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(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.3
10B	Aerosol air freshener	5.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.060
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 4-ethylguaiacol the basis was a subchronic reference dose of 3 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 1700 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, 4-ethylguaiacol does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of 4-ethylguaiacol; however, read-across can be made to guaiacol (CAS # 90-05-1; see Section VI). The mutagenic activity of guaiacol has been evaluated in a bacterial reverse mutation assay using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with guaiacol 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 (Pool and Lin, 1982). Under the conditions of the study, guaiacol was not mutagenic in the Ames test. In addition, these results were confirmed in additional Ames studies (Haworth et al., 1983). *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with guaiacol at concentrations up to 10000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9. Under the conditions of the study, guaiacol was not mutagenic in the Ames test, and this can be extended to 4-ethylguaiacol. As an additional WoE, another Ames study, equivalent to OECD TG 471 and conducted using 3 test strains (TA98, TA100, and TA102) in the presence and absence of metabolic activation was also concluded to be negative (ECHA, 2011).

The clastogenic activity of guaiacol 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 the oral route to groups of male and female NMRI mice. Doses of 125, 250, or 500 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 and 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011). Under the conditions of the study, guaiacol was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to 4-ethylguaiacol.

Based on the data available, *guaiacol* does not present a concern for genotoxic potential, and this can be extended to 4-ethylguaiacol.

Additional References: Aeschbacher (1989); Ferretti et al., 1977; Florin et al., 1980; Nestmann et al., 1980; Nestmann and Lee, 1983; Rapson et al., 1980; Douglas et al., 1980; Haworth et al., 1983; Jansson et al., 1986; Stich et al., 1981; Tsutsui et al., 1987; Ohshima et al., 1989; Rosin (1984); Someya et al., 2008; Miyachi and Tsutsui, 2005; Hamaguchi and Tsutsui, 2000; Hikiba et al., 2005.

Literature Search and Risk Assessment Completed On: 06/09/21.

11.1.2. Repeated dose toxicity

The MOE is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data available for 4-ethylguaiacol. Read-across material eugenol and WoE-material 2-ethoxy-4-methylphenol (CAS # 97-53-0 and CAS # 2563-07-7, respectively; see Section VI) have sufficient repeated dose toxicity data. However, the NOAEL for repeated toxicity of 4-ethylguaiacol was determined from the available repeated dose toxicity data on eugenol (CAS # 97-53-0) since the studies were of longer duration, and hence provided a more robust conclusion. Thus, data on materials 2-ethoxy-4-methylphenol (CAS # 2563-07-7) are considered as WoE.

The NOAEL for repeated dose toxicity of eugenol was determined to be 300 mg/kg/day from a dietary 13-week subchronic toxicity study conducted in rats, based on reduced body weights (NTP, 1983).

The Expert Panel for Fragrance Safety* has reviewed the carcinogenicity data on eugenol. In a subchronic study, eugenol was administered in the diet of F344/N rats (10/sex/group) at concentrations of 0, 800, 1500, 3000, 6000, or 12500 ppm (equivalent to doses of 0, 40, 75, 150, 300, or 625 mg/kg/day) for 13 weeks. In carcinogenicity studies, eugenol was administered in the diet of F344/N rats (50/sex/group) at concentrations of 0, 3000 (males only), 6000 (males and females), or 12500 ppm (females only) (equivalent to doses of 0, 150, 300, or 625 mg/kg/day) for 103 weeks, as well as in the diet of B6C3F1 mice (50/sex/group) and at concentrations of 0, 3000, or 6000 ppm (equivalent to doses of 0, 450, or 900 mg/kg/day) for 103 weeks. The US NTP concluded that hepatocellular tumors observed following eugenol administration were considered to be associated with the dietary administration of eugenol, but because of the lack of a dose-response effect in male mice and the marginal combined increases in female mice, there was equivocal evidence of carcinogenicity (NTP, 1983). It was not carcinogenic to rats (NTP, 1983). Hepatotoxicity might have played a role in the development of hepatic tumors in B6C3F1 mice, which are sensitive to the development of liver tumors by non-genotoxic mechanisms. The total systemic exposure to eugenol is 0.019 mg/kg/day, which is more than 23600 times lower than the lowest dose level in the mouse NTP study.

Therefore, the 4-ethylguaiacol MOE for the repeated dose toxicity endpoint can be calculated by dividing the eugenol NOAEL in mg/kg/day by the total systemic exposure to 4-ethylguaiacol, 300/0.000012 or 25000000.

In addition, the total systemic exposure to 4-ethylguaiacol (0.012 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) of a Cramer Class I material for the repeated dose toxicity endpoint at the current level of use.

Derivation of subchronic reference dose (RfD)

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a subchronic RfD of 3 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default

MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for 4-ethylguaiacol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 300 mg/kg/day by the uncertainty factor, 100 = 3 mg/kg/day.

WoE

In an OECD 407/GLP-compliant subchronic toxicity study, 5 CD rats/sex/group were administered 2-ethoxy-4-methylphenol orally via gavage at doses of 0 (corn oil), 60, 150, and 600 mg/kg/day for 28 days. No treatment-related mortalities were reported at any dose level. Clinical signs of toxicity reported after dosing were hunched posture, abnormal gait (waddling), and salivation in all the treatment groups throughout the study duration. At doses of 150 and 600 mg/kg/day, all animals demonstrated piloerection combined with lethargy from week 2. Mean body weight and bodyweight gains significantly decreased in male rats in the 150 mg/kg/day group (week 1) as well as in female rats in the 600 mg/kg/day group (week 4). Although decreased body weight and bodyweight gain were combined with minimally reduced food consumption in both 150 and 600 mg/kg/day dose groups throughout the study, the changes were not statistically significant and are indicative of treatment-related mild anorexia. With the exception of mean corpuscular hemoglobin concentration in females receiving the 600 mg/kg/day dose for 4 weeks, no treatment-related hematological changes were reported. Mild anemia in females represented by lower mean corpuscular hemoglobin concentration is considered a treatment-related effect despite being sex-specific. Serum biochemistry analysis in all animals at the end of the 4-week treatment reported elevated serum levels of glucose, cholesterol, and triglycerides in females and significantly increased levels of glutamic-pyruvic transaminase and glutamic-oxaloacetic transaminase levels in male animals in the highest dose group. These biochemical changes were accompanied by dose-dependent (statistically insignificant) changes in alkaline phosphatase levels in either sex. Although no histopathological changes in the liver were reported, the clinical chemistry findings are indicative of minimal hepatotoxicity. In addition, at 600 mg/kg/day, relative liver weights in males decreased while relative liver weight increased in 1/5 females of the same dose group. The alterations in liver weight were not statistically significant; these were considered treatment-related changes due to associated biochemical changes. No treatment-related histopathological changes of kidneys, spleen, liver, adrenal gland, or heart were reported at any dose in either sex. Based on treatment-related clinical signs observed in all treatment groups, a NOAEL could not be established from this study. Hence, a LOAEL of 60 mg/kg/day was used for repeated dose toxicity endpoint (RIFM, 1989a).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 4-ethylguaiacol or any read-across materials. The total systemic exposure to 4-ethylguaiacol 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 4,9-dodecadienenitrile, (4Z,9Z)- or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.012 μg/kg/day) is below the TTC for 4,9-dodecadienenitrile, (4Z,9Z)- (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.4. Skin sensitization

Based on the data on read-across material 2-methoxy-4-propylphenol (CAS # 2785-87-7), 4-ethylguaiacol is considered a skin sensitizer with a defined NESIL of 1700 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 4-ethylguaiacol. Based on the existing data and read-across material 2-methoxy-4-propylphenol (CAS # 2785-87-7; see Section VI), 4-ethylguaiacol is considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0). Read-across material 2-methoxy-4-propylphenol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) (Natsch, 2007, 2008, 2013a). However, read-across material 2-methoxy-4-propylphenol was found to be positive in KeratinoSens and U937-CD86 tests (Emter et al., 2010; Natsch, 2013a; Piroird et al., 2015). In a murine local lymph node assay (LLNA), read-across material 2-methoxy-4-propylphenol was found to be sensitizing with an EC3 value of 6.8% (1700 μg/cm^2) (Roberts et al., 2007; ECHA, 2017a). In guinea pig maximization tests, read-across material 2-methoxy-4-propylphenol presented reactions indicative of sensitization at 100% (RIFM, 1989b; RIFM et al., 1988; ECHA, 2017a). However, in a guinea pig closed epicutaneous test (CET) with read-across material 2-methoxy-4-propylphenol, no reactions indicative of sensitization were observed (Itoh, 1982). In a human maximization test, no skin sensitization reactions were observed with read-across material 2-methoxy-4--propylphenol at 8% (5520 μg/cm^2) (RIFM, 1977). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 1.5% or 1771 μg/cm^2 of read-across material 2-methoxy-4-propylphenol in 1:3 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 107 volunteers (RIFM, 2015).

Based on the available data on read-across material 2-methoxy-4-propylphenol, summarized in Table 1, 4-ethylguaiacol is considered to be a moderate skin sensitizer with a defined NESIL of 1700 μg/cm^2. Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a subchronic RfD of 3 mg/kg/day.

Additional References: Natsch (2013b); McKim et al., 2010; RIFM, 1988b, Barratt and Basketter, 1992; Roberts et al., 2007.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, 4-ethylguaiacol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. The available UV/Vis spectra (OECD TG 101) for 4-ethylguaiacol 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}) of concern for phototoxic effects (Henry et al., 2009). Based on UV/Vis absorption spectra, 4-ethylguaiacol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available UV/Vis spectra (OECD TG 101) for 4-ethylguaiacol indicate minor absorbance between 290 and

Table 1
Data summary for 2-methoxy-4-propylphenol as read-across material for 4-ethylguaiacol.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
1700	Moderate	1771	5520	NA	1700

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

700 nm. The molar absorption coefficient for wavelengths between 290 and 700 nm is below the benchmark (1000 L mol^{-1} • cm^{-1}) of concern for phototoxic and photoallergenic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4-ethylguaiacol 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 4-ethylguaiacol. Based on the Creme RIFM Model, the inhalation exposure is 0.000034 mg/day. This exposure is 41176 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: 06/24/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4-ethylguaiacol 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, 4-ethylguaiacol 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 4-ethylguaiacol as being possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current VoU (2015), 4-ethylguaiacol does not present a risk to the aquatic compartment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 4-Ethylguaiacol has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.35	2.35
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

The RIFM PNEC is 0.1018 μg/L. The revised PEC/PNECs for the EU and NA are not applicable. The material was cleared at the screening-

		(mg/L)				
RIFM Framework Screening-level **(Tier 1)**	101.8			1000000	0.1018	

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: 06/25/21.

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
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 10/06/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112854.

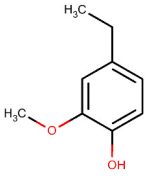
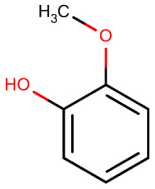
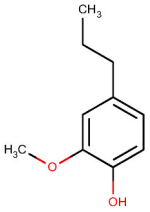
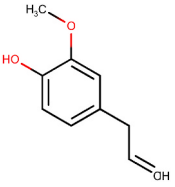
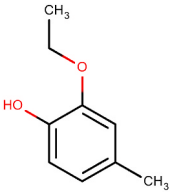
Appendix

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, 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 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 material 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	WoE Material
Principal Name	4-Ethylguaiacol	Guaiacol	2-Methoxy-4-propylphenol	Eugenol	2-Ethoxy-4-methylphenol
CAS No.	2785-89-9	90-05-1	2785-87-7	97-53-0	2563-07-7
Structure					
Similarity (Tanimoto Score)		0.47	0.87	0.86	0.70
Endpoint		• Genotoxicity	• Skin sensitization	• Repeated dose toxicity	• Repeated dose toxicity
Molecular Formula	$C_9H_{12}O_2$	$C_7H_8O_2$	$C_{10}H_{14}O_2$	$C_{10}H_{12}O_2$	$C_9H_{12}O_2$
Molecular Weight (g/mol)	152.19	124.14	166.22	164.204	152.19
Melting Point (°C, EPI Suite)	−7.00	32.00	61.64	−9.10	51.22
Boiling Point (°C, EPI Suite)	236.50	205.00	265.51	255.00	248.39
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.31	13.73	0.28	2.93E+00	0.93
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	693.80	18700.00	228.00	2.46E+03	693.80
Log K_{OW}	2.38	1.32	2.87	2.49	2.38
J_{max} (μg/cm²/h, SAM)	25.79	266.39	12.17	81.29	25.79
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	0.00	0.12	0.01	2.02E-01	0.00
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found			
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals| Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Alkyl phenols| Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Hydroquinones	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals| Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Hydroquinones			
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	Phenol Type Compounds	Phenol Type Compounds			
Repeated Dose Toxicity					
Repeated Dose (HESS)	Not categorized			Not categorized	Phenacetin (Hepatotoxicity) Alert| Phenacetin (Renal toxicity) Alert
Skin Sensitization					
Protein Binding (OASIS v1.1)	No alert found		No alert found		
Protein Binding (OECD)	No alert found		No alert found		
Protein Binding Potency	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)		
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found		No alert found		
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Michael Acceptor identified.		Alert for Michael Acceptor identified.		
Metabolism					

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	WoE Material
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on 4-ethylguaiacol (CAS # 2785-89-9). 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, 2-methoxy-4-propylphenol (CAS # 2785-87-7), guaiacol (CAS # 90-05-1), and eugenol (CAS # 97-53-0) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 2-Methoxy-4-propylphenol (CAS # 2785-87-7) was used as a read-across analog for the target material 4-ethylguaiacol (CAS # 2785-89-9) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to a class of substituted phenols.
  - o The target material and the read-across analog share a phenol ring with a methoxy group in the ortho position.
  - o The key difference between the target material and the read-across analog is that the target material has an ethyl group para to the phenol, whereas the read-across has a propyl group at the same position. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The difference between the structures that affect the Tanimoto score is toxicologically insignificant.
  - o The physical–chemical properties of the target material 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 material and the read-across analog.
  - o Both the target material and the read-across analog have an alert for Michael addition reaction by the Toxtree reactive domain model. The data described in the skin sensitization section confirm that the read-across analog is a skin sensitizer. Therefore, *in silico* alerts are consistent with the data.
  - o The target material 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.
- Guaiacol (CAS # 90-05-1) was used as a read-across analog for the target material 4-ethylguaiacol (CAS # 2785-89-9) for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of substituted phenols.
  - o The target material and the read-across analog share a phenol ring with a methoxy group in the ortho position.
  - o The key difference between the target material and the read-across analog is that the target material has an ethyl group para to the phenol, whereas the analog lacks a para substituent. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The difference between the structures that affect the Tanimoto score is toxicologically insignificant.
  - o The physical–chemical properties of the target material 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 material and the read-across analog.
  - o Both the target and the read-across analog have an alert of being Michael acceptors in nucleophilic addition. However, the mechanism differs in both compounds since the target has an ethyl group in the para position with respect to the OH group while the read-across analog lacks any substituent in that position. Consequently, for the target, oxidation by cytochrome P450 to a quinone methide followed by Michael addition has been suggested to be the primary route of DNA binding. For the read-across analog, hydroquinones have been shown to be oxidized to quinones which can then bind to DNA via a Michael addition mechanism. Methoxy quinones undergo demethylation to produce the corresponding hydroquinone. Hydroquinones are expected to be more reactive compared to the quinone methides, making the read-across analog more reactive compared to the target material. The data described in the genotoxicity section confirm that the read-across analog does not pose a concern for genetic toxicity. Therefore, the predictions are superseded by data.
  - o The target material 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.
- Eugenol (CAS # 97-53-0) was used as a read-across analog for the target material 4-ethylguaiacol (CAS # 2785-89-9) for the repeated dose toxicity endpoint.
  - o The target material and the read-across analog belong to a class of substituted phenols.
  - o The key difference between the target material and the read-across analog is that the read-across analog has a vinyl group on the para substitution to the phenol, whereas the target material has saturated ethyl substitution at the same position. The vinyl group in the read-across analog can undergo epoxidation and show a mode of action via epoxide-created radical formation. This is not predicted for the target material. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have a greater potential for toxicity as compared to the target material.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material 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 material and the read-across analog.

- 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.

- 2-Ethoxy-4-methylphenol (CAS # 2563-07-7) was used as a WoE material for the target material 4-ethylguaiacol (CAS # 2785-89-9) for the repeated dose toxicity endpoint.
  - The target material and the read-across analog belong to a class of substituted phenols.
  - The key difference between the target material and the WoE material is that the WoE material has a methyl group para to the phenol, whereas the target material has an ethyl substitution at the same position. Moreover, the target has a methoxy group ortho to the phenol whereas the read-across analog has an ethoxy group ortho to the phenol. These structural differences are toxicologically insignificant.
  - Similarity between the target material and the WoE material is indicated by the Tanimoto score. The differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the WoE material are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The HESS categorization scheme has a phenacetin (renal toxicity) alert for the WoE material. The target material does not have this alert. This difference is due to the fact that the read-across analog shares more than 50% similarity with phenacetin. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. Data supersedes predictions in this case.
  - The target material and the WoE material are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the WoE material and the target material.

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