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RIFM fragrance ingredient safety assessment, 2-ethoxy-4-methylphenol, CAS Registry Number 2563-07-7

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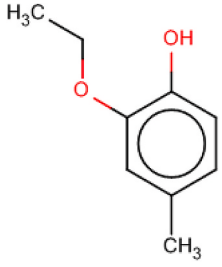

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

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Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure

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(*continued*)

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

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

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

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

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

2-Ethoxy-4-methylphenol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-ethoxy-4-methylphenol is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across material isoeugenol (CAS # 97-54-1) provide a calculated MOE >100 for the developmental and reproductive toxicity endpoint. Data from 2-ethoxy-4-methylphenol provided a No Expected Sensitization Induction Level (NESIL) of 230 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; 2-ethoxy-4-methylphenol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 2-ethoxy-4-methylphenol is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 2-ethoxy-4-methylphenol 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., PEC/PNEC [Predicted Environmental Concentration/Predicted No Effect Concentration]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1984a; RIFM, 1989a)
Repeated Dose Toxicity: NOAEL = 2 mg/kg/day.	RIFM (1989b)
Developmental and Reproductive Toxicity:	
Developmental toxicity: NOAEL = 250 mg/kg/day. Reproductive toxicity: NOAEL = 230 mg/kg/day.	(NTP, 1999; NTP, 2002)
Skin Sensitization: NESIL = 230 μg/cm^2.	(RIFM, 2004; RIFM, 2007)

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Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database; RIFM, 1986a; RIFM, 1985)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 83.7% (OECD 301B)	RIFM (1993a)
Bioaccumulation: Screening-level: 17.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 75.4 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: 75.40 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.07540 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** 2-Ethoxy-4-methylphenol
2. **CAS Registry Number:** 2563-07-7
3. **Synonyms:** 2-Ethoxy-p-cresol; 4-Methyl-2-ethoxyphenol; Phenol, 2-ethoxy-4-methyl-; Supravanil; 2-Ethoxy-4-methylphenol
4. **Molecular Formula:** $C_9H_{12}O_2$
5. **Molecular Weight:** 152.19
6. **RIFM Number:** 6294
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 503.5 K (230.3 °C) (RIFM, 1991a), 248.39 °C (EPI Suite)
2. **Flash Point:** >93 °C (GHS)
3. **Log K_{OW}:** ≥2.5 (RIFM, 1990a), 2.38 (EPI Suite)
4. **Melting Point**: melting range = 303.5 K (30.3 °C) −305.8 K (32.6 °C) (RIFM, 1991b), 51.22 °C (EPI Suite)
5. **Water Solubility:** 693.8 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00384 mm Hg @ 20 °C (EPI Suite v4.0), 0.00699 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A pale yellow to yellow, clear liquid to solid with a medium, vanilla, woody, spicy, guaiacol odor while at 10% or less in dipropylene glycol.*

*http://www.thegoodscentscompany.com/data/rw1096541.html, retrieved 05/21/15.

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.024% (RIFM, 2014)
2. **Inhalation Exposure*:** 0.000064 mg/kg/day or 0.0046 μg/day (RIFM, 2014)

3. **Total Systemic Exposure**:** 0.00050 mg/kg/day (RIFM, 2014)

*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 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; 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

1. **Cramer Classification:** Class III, High (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
III*	II	II

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** Isoeugenol (CAS # 97-54-1)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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 (discrete chemical) or composition (NCS)

2-Ethoxy-4-methylphenol 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. This is a partial list.

9. REACH dossier

Dossier available; accessed 10/03/18 (ECHA, 2013).

10. Conclusion

The maximum acceptable concentrations[a] in the finished products for 2-ethoxy-4-methylphenol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.0087
2	Products applied to the axillae	0.0053
3	Products applied to the face/body using fingertips	0.017
4	Products related to fine fragrances	0.099
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.025
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.017
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.025
5D	Baby cream, oil, talc	0.0058
6	Products with oral and lip exposure	0.0087
7	Products applied to the hair with some hand contact	0.044
8	Products with significant ano-genital exposure (tampon)	0.0058
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.052
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.052
10B	Aerosol air freshener	0.052
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0058
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	4.2

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 2-ethoxy-4-methylphenol, the basis was the reference dose of 0.02 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 230 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).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, 2-ethoxy-4-methylphenol does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2-ethoxy-4-methylphenol has been evaluated in a bacterial reverse mutation assay using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 2-ethoxy-4-methylphenol in ethanol 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, 1984a). Under the conditions of the study, 2-ethoxy-4-methylphenol was not mutagenic in the Ames test.

The clastogenicity of 2-ethoxy-4-methylphenol was assessed in an *in vitro* chromosome aberration study. Chinese hamster ovary cells were

treated with 2-ethoxy-4-methylphenol in dimethyl sulfoxide (DMSO) at concentrations up to 50 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test item, either with or without S9 metabolic activation (RIFM, 1989a). Under the conditions of the study, 2-ethoxy-4-methylphenol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the available data, 2-ethoxy-4-methylphenol does not represent a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/17/18.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 2-ethoxy-4-methylphenol. 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 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 with dose-dependent (statistically insignificant) changes in ALP 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, 1989b).

A default safety factor of 10 was used when deriving a NOAEL from the LOAEL. The safety factor has been approved by the Expert Panel for Fragrance Safety*. **Thus, the initial derived NOAEL for the repeated dose toxicity data is 60/10 or 6 mg/kg/day.**

An additional default safety factor of 3 was used when deriving a NOAEL from the 28-day study. The safety factor has been approved by the Expert Panel for Fragrance Safety*. **Thus, the final derived NOAEL for the repeated dose toxicity data is 6/3 or 2 mg/kg/day**.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Therefore, the 2-ethoxy-4-methylphenol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-ethoxy-4-methylphenol NOAEL by the total systemic exposure for 2-ethoxy-4-methylphenol, 2/0.0005 or 4000.

11.1.2.2. Derivation of reference dose (RfD). The RIFM Criteria Document (Api et al., 2015) calls for a default margin of exposure of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for 2-ethoxy-4-methylphenol was calculated by dividing the lowest NOAEL (from the Repeated Dose Toxicity and the Developmental and Reproductive Toxicity sections) of 2 mg/kg/day by the uncertainty factor, 100 = 0.02 mg/kg/day. 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, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.02 mg/kg/day.

In addition, the total systemic exposure to 2-ethoxy-4-methylphenol (0.5 μg/kg bw/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

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

11.1.3. Developmental and reproductive toxicity

The margin of exposure for 2-ethoxy-4-methylphenol is adequate for the developmental and reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are insufficient developmental and reproductive toxicity data on 2-ethoxy-4-methylphenol. Read-across material isoeugenol (CAS # 97-54-1; see Section VI) 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) were 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 the 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 the 1000 mg/kg/day dose group pups. The LOAEL for maternal toxicity was considered to be 250 mg/kg/day, based on reduced body weight, gestational weight gain, and aversion to treatment. 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 post-natal 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, and 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 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 and developmental toxicity 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, 1999; Layton et al., 2001).

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

The 2-ethoxy-4-methylphenol MOE for the developmental toxicity endpoint can be calculated by dividing the isoeugenol NOAEL in mg/kg/day by the total systemic exposure to 2-ethoxy-4-methylphenol, 250/0.0005 or 500000.

The 2-ethoxy-4-methylphenol MOE for the reproductive toxicity endpoint can be calculated by dividing the isoeugenol NOAEL in mg/kg/day by the total systemic exposure to 2-ethoxy-4-methylphenol, 230/0.0005 or 460000.

In addition, the total systemic exposure to 2-ethoxy-4-methylphenol (0.5 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

Additional References: RIFM, 1989b.

Literature Search and Risk Assessment Completed On: 11/07/17.

11.1.4. Skin sensitization

Based on the existing data, 2-ethoxy-4-methylphenol is considered a skin sensitizer with a defined NESIL of 230 μg/cm^2.

11.1.4.1. Risk assessment. The chemical structure of this material indicates that 2-ethoxy-4-methylphenol would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD toolbox v4.2). In a murine local lymph node assay (LLNA), 2-ethoxy-4-methylphenol was found to be non-sensitizing up to 5% (RIFM, 2012). In 3 guinea pig maximization tests with 2-ethoxy-4-methylphenol at 50% in acetone/PEG, 5%, and 5% in Vaseline, reactions indicative of sensitization were observed (RIFM, 1989c; RIFM, 1984b; RIFM, 1986b). Additionally, in 2 confirmatory human repeat insult patch tests (HRIPTs), reactions indicative of sensitization were observed in 17/32 and 23/29 volunteers when 2-ethoxy-4-methylphenol at 2% (2362 μg/cm^2) in 3:1 diethyl phthalate:ethanol (DEP:EtOH) was tested (RIFM, 2003a; RIFM, 2003b). However, in 2 other HRIPTs, 2-ethoxy-4-methylphenol did not present reactions indicative of sensitization when tested at 0.2% (236 μg/cm^2) in 3:1 DEP:EtOH in any of the 52 and 56 volunteers (RIFM, 2004; RIFM, 2007). Each of these 2 studies was conducted with less than 100 volunteers, deviating from the standard HRIPT protocol (Politano and Api, 2008). However, both HRIPTs followed an identical protocol and were conducted using the same concentrations and the same patches. The total number of volunteers in both studies is 108. Therefore, these 2 studies were considered together to derive a NESIL of 230 μg/cm^2.

Based on the available data, summarized in Table 1, 2-ethoxy-4-methylphenol is considered to be a moderate skin sensitizer with a defined NESIL of 230 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. (2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.02 mg/kg/day.

Additional References: RIFM, 1989c.

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

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and *in vivo* data, 2-ethoxy-4-methylphenol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In an *in vivo* phototoxicity test, a solution of 10% for 2-ethoxy-4-methylphenol applied to the backs of rabbits did not result in skin reactions after exposure to UV light (RIFM, 1986a). In an *in vivo* photosensitization study, no reactions were seen in guinea pigs challenged with a 10% solution of 2-ethoxy-4-methylphenol and exposed to UV light (RIFM, 1985). Based on *in vivo* data, 2-ethoxy-4-methylphenol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant 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: 11/04/18.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 2-ethoxy-4-methylphenol is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-ethoxy-4-methylphenol. Based on the Creme RIFM Model, the inhalation exposure is 0.0046 mg/day. This exposure is 102.2 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References:None.

Literature Search and Risk Assessment Completed On: 10/23/18.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-ethoxy-4-methylphenol was performed following the RIFM Environmental Framework (Salvito et al.,

Table 1
Data summary for 2-ethoxy-4-methylphenol.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
1250[1]	NA	236	NA	2362	230

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

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

11.2.1.1. Risk assessment. Based on the current VoU (2015), 2-ethoxy-4-methylphenol does not present risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 1990b: The modified Sturm test was conducted according to the OECD 301B method to determine the ready biodegradability of the test material. An aqueous medium inoculated with active sludge was used. The test duration was 28 days. Biodegradation of 55% was observed.

RIFM, 1993b: The ready and ultimate biodegradability of the test material was evaluated using the sealed vessel test (OECD Guideline 301B). The source of the inoculum was secondary effluent from an unacclimatized activated sludge plant. Biodegradation by day 28 was 83.7%.

RIFM, 1993a: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test following the OECD 301B method. Under the conditions of the study, biodegradation of 83.7% was observed by day 28.

11.2.1.2.2. Ecotoxicity. RIFM, 1990c: A 96-h fish (*Cyprinus carpio*) acute study was conducted according to the OECD 203 method. The 96-h LC50 for the test material to carp, based on nominal test concentrations, was reported to be 42 mg/L.

RIFM, 1990d: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 for immobility of *Daphnia magna* was reported to be between 1.0 and 1.8 mg/L.

RIFM, 1998: A static algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 for growth inhibition was 24.5 mg/L.

11.2.1.2.3. Other available data. 2-Ethoxy-4-methylphenol has been registered for REACH with no additional data at this time.

11.2.1.2.4. Risk assessment refinement. Since 2-ethoxy-4-methylphenol 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.5	2.5
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.07540 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/01/18.

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**

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	75.4			1,000,000	0.0754	

- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** 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 02/26/19.

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.2020.111657.

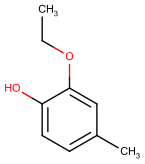
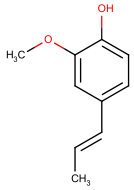
Appendix

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
Principal Name	2-Ethoxy-4-methylphenol	Isoeugenol
CAS No.	2563-07-7	97-54-1
Structure		
Similarity (Tanimoto Score)		0.63
Read-across Endpoint		• Developmental and Reproductive Toxicity
Molecular Formula	$C_9H_{12}O_2$	$C_{10}H_{12}O_2$
Molecular Weight	152.19	164.20
Melting Point (°C, EPI Suite)	51.22	33.50
Boiling Point (°C, EPI Suite)	248.39	266.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.932	1.80
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.38	3.04
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	693.38	810.00
J_{max} (μg/cm^2/h, SAM)	157.13	79.64
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.92E-003	2.70E-003
Developmental and Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Weak binder, OH group	• Weak binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	• Non-Toxicant (moderate reliability)	• Non-Toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-ethoxy-4-methylphenol (CAS # 2563-07-7). 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, isoeugenol (CAS # 97-54-1) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Isoeugenol (CAS # 97-54-1) was used as a read-across analog for the target material 2-ethoxy-4-methylphenol (CAS # 2563-07-7) for the developmental and reproductive toxicity endpoint.

o The target substance and the read-across analog are structurally similar and belong to a class of substituted alkylphenol ethers.
oThe target substance and the read-across analog share a similar phenol ether structure.
oThe key difference between the target substance and the read-across analog is that the target substance has a methyl substitution on the 4 position, hydroxyl para to the phenol, whereas the read-across analog has a propenyl group at the same position. This structural difference is toxicologically insignificant for the developmental and reproductive toxicity endpoint.
oThe 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.
oThe physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
oAccording to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
oThe target substance and the read-across analog have an alert of being a weak ER binder due to the presence of an OH group and the possibility of formation of hydroquinone. The data described in the developmental and reproductive toxicity section confirm that the margin of exposure is adequate at the current level of use. Therefore, the predictions are superseded by data.
oThe target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
oThe structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree.
1N,2N,3N,5N,6N,7N,16N,17N, 19N,23Y,27Y,28N,30Y,31N,32N,22N,33N, III.
Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.

Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.

Q6. Benzene derivative with certain substituents? No.

Q16. Common terpene? (see Cramer et al., 1978 for a detailed explanation) No.

Q17. Readily hydrolyzed to a common terpene? No.

Q19. Open chain? No.

Q23. Aromatic? Yes.

Q27. Rings with substituents? Yes.

Q28. More than one aromatic ring? No.

Q30. Aromatic ring with complex substituents? Yes.

Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No.

Q32. Contains only the functional groups listed in Q30 or Q31 and either a) a single fused non-aromatic carbocyclic ring or b) aliphatic substituent chains longer than 5 carbon atoms or c) a polyoxyethylene ($n \geq 4$) on the aromatic or aliphatic side chain? No.

Q22. A common component of food? No.

Q33. Has a sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? No. Class High, Class III.

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