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Short Review

RIFM fragrance ingredient safety assessment, *p*-ethylphenol, CAS Registry Number 123-07-9

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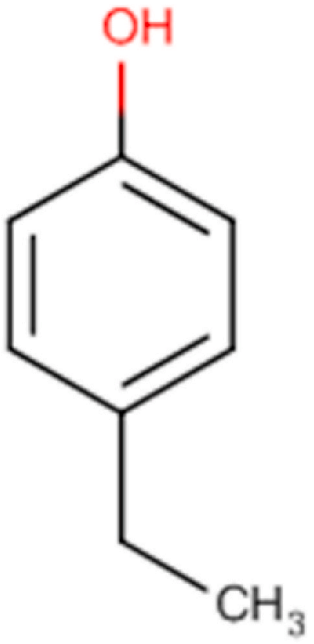

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use, but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food

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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.

p-Ethylphenol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Weight of evidence (WoE) from *p*-ethylphenol and read-across material 4-vinylphenol (CAS # 2628-17-3) show that *p*-ethylphenol is not expected to be genotoxic. Data on *p*-ethylphenol provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; *p*-ethylphenol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to *p*-ethylphenol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; *p*-ethylphenol 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. (ECHA REACH Dossier: 4-Ethylphenol; ECHA, 2018; ECHA REACH Dossier: Cresol; ECHA, 2011)

Repeated Dose Toxicity: NOAEL = 100 mg/kg/day. (Takahashi, 2006)

Reproductive Toxicity: Developmental toxicity: NOAEL = 100 mg/kg/day. Fertility: NOAEL = 100 mg/kg/day. (ECHA REACH Dossier: 4-Ethylphenol; ECHA, 2018)

Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 87% (OECD 310; Headspace Test) (ECHA REACH Dossier: 4-Ethylphenol; ECHA, 2018)

Bioaccumulation: Screening-level: 23.4 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish Lethal Concentration 50 (LC50): 51.56 mg/L (RIFM Framework; Salvito, 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, 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 51.56 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.05156 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** *p*-Ethylphenol
2. **CAS Registry Number:** 123-07-9
3. **Synonyms:** 4-Ethylphenol; 4-Hydroxyethylbenzene; Phenol, 4-ethyl-; *p*-Ethyl phenol; *p*-Ethylphenol
4. **Molecular Formula:** $C_8H_{10}O$
5. **Molecular Weight:** 122.16
6. **RIFM Number:** 6249
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 210.68 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 2.58 (Patel, 2002), LogK pdms/w = 0.887 (n = 12), 2.47 (Smith, 2002), 2.50 (Smith, 2002), Log Kow = 2.50 (Ohlenbusch and Frimmel, 2001), 2.55 (EPI Suite)
4. **Melting Point**: 27.13 °C (EPI Suite)
5. **Water Solubility:** 2346 mg/L (EPI Suite)
6. **Specific Gravity:** 1.01 (FMA)
7. **Vapor Pressure:** 0.0245 mm Hg at 20 °C (EPI Suite v4.0), 0.02 mm Hg at 20 °C (FMA), 0.0428 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v2.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0026% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0000065 mg/kg/day or 0.00048 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00080 mg/kg/day (RIFM, 2019)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** 4-Vinylphenol (CAS # 2628-17-3)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   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

No relevant data available for inclusion in this safety assessment.
Additional References: None.

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

p-Ethylphenol is reported to occur in the following foods by the VCF*:

Beer
Cider (apple wine)
Coffee
Fish
Olive (*Olea europaea*)
Rum
Salami
Sherry
Vinegar
Wine

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

9. REACH dossier

Available; accessed 11/01/19 (ECHA, 2018).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, *p*-ethylphenol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of *p*-ethylphenol has been evaluated in a bacterial reverse mutation assay conducted in

compliance with GLP regulations and in accordance with OECD TG 471 using the standard preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with *p*-ethylphenol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2018). Under the conditions of the study, *p*-ethylphenol was not mutagenic in the Ames test.

The clastogenicity of *p*-ethylphenol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung cells were treated with *p*-ethylphenol in DMSO at concentrations up to 800 μg/mL in the presence and absence of metabolic activation. Statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cell groups within the 6-h treatment with S9 and 24-h treatment without S9 treatment conditions (ECHA, 2018). Under the conditions of the study, *p*-ethylphenol was considered to be clastogenic in the *in vitro* chromosome aberration assay. However, the cell line used in the study was p53-deficient and may lead to a biologically non-relevant response (Fowler, 2012). Additionally, *in vivo* data on a similar material, which also had some adverse data in the traditional *in vitro* battery, showed negative responses in more biologically relevant *in vivo* studies. In an *in vivo* micronucleus test according to OECD TG 474, 4-vinylphenol tested negative, since no structural and/or numerical chromosomal damage in the erythrocytes of treated mice was observed. Taken, together, it can be concluded that *p*-ethylphenol may not possess any clastogenic potential.

Based on the data available, *p*-ethylphenol may not present a concern for genotoxic potential.

Additional References: ECHA, 2011.

Literature Search and Risk Assessment Completed On: 01/02/19.

11.1.2. Repeated dose toxicity

The MOE for *p*-ethylphenol 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 for the target material. In an OECD TG 407, GLP-compliant subchronic repeated dose study, groups of 7 SPF Crj:CD(SD)IGS rats/sex/dose were administered the test material via gavage at doses of 0, 100, 300, or 1000 mg/kg/day for 28 days. In addition, recovery groups of 7 rats/sex/dose were maintained for 2 weeks at the 0 and 1000 mg/kg/day doses. Rats were examined for general body condition, food consumption, urinalysis, hematology, blood biochemistry, necropsy findings, organ weights, and histopathological findings. No treatment-related mortality occurred throughout the study period. Body weights were lower in both sexes at the high dose. Liver effects included increased relative liver weights in males at the mid dose (300 mg/kg/day) and both sexes at the high dose (1000 mg/kg/day). Increased ALT levels were seen in high-dose males only, while increased total cholesterol levels were seen in high-dose females only. Kidney effects included increased relative kidney weights in males at the high dose. However, these changes were likely secondary to the decreased body weights in both sexes. Forestomach lesions were seen in 1 male at the mid dose and most or all individuals of both sexes at the high dose. However, forestomach effects are not relevant to human health. Adverse clinical signs (staggering gait, a lateral position, and soiled perigenital fur) were also observed in both sexes at the high dose. Based on decreased body weights and adverse clinical signs seen in both sexes at 1000 mg/kg/day, the NOAEL for this study was considered to be 300 mg/kg/day (Takahashi, 2006; also available in ECHA, 2018).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. Thus, the derived NOAEL for the repeated dose toxicity data is 300/3 or 100 mg/kg/day.

Therefore, the MOE can be calculated by dividing the NOAEL (in mg/kg/day) for 3-ethylphenol by the total systemic exposure (in mg/kg/day) of 3-ethylphenol, 100/0.0008 or 125000.

In addition, the total systemic exposure to 3-ethylphenol (0.8 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose endpoint of a Cramer Class I material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/01/19.

11.1.3. Reproductive toxicity

The MOE for *p*-Ethylphenol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data for the target material. In a GLP-compliant, OECD 421 reproduction/developmental toxicity study, 13 Sprague Dawley (SD) rats/sex/dose were administered 4-ethylphenol via gavage at doses at 0, 30, 100, and 300 mg/kg/day for 42 days (males) or during the 2-week premating period, the mating period, and the period from day 1 of pregnancy to day 4 of postnatal lactation (females). Two females from the high-dose (300 mg/kg) group died during labor on day 22 or 23 of pregnancy. These deaths were considered to be treatment-related. One female from the 300 mg/kg group did not show any nursing behavior (gathering or licking the newborns upon completion of delivery). Her offspring had no milk spots (a sign of maternal milk pooling) on the abdomen, suggesting that they were not being breastfed. All offspring from this female died on day 1 of lactation. All offspring from another high-dose female died on day 0 of lactation, with evidence of damage resulting from eating by the dam on many dead bodies of the offspring. Clinical findings suggested intense stress, cardiovascular disorders, anemia, and hepatic/renal dysfunction. These findings suggest that these dams died prematurely or were unable to maintain nursing due to poor condition resulting from the interaction of the treatment with stress related to pregnancy and delivery. One female from the mid-dose (100 mg/kg/day) group did not give birth. Another mid-dose female was not confirmed to deliver until day 25 of pregnancy; necropsy revealed implantation scars (1 right, 1 left). There were corpora lutea (6 right, 11 left) but no dead fetus larger than a residual placenta, suggesting that embryos had been absorbed during the early stages of pregnancy. However, because no other females exhibited increased early embryo absorption and there was no difference in implantation index or delivery index, these effects were not considered to be treatment-related. One dam from the low-dose (30 mg/kg/day) group showed decreasing body weight during the lactation period, with very low food consumption. Her offspring began to die on day 2 of lactation, and the remaining offspring were unable to gain weight. The necropsy and histopathological examinations suggested that this dam had renal dysfunction. However, this effect was not considered to be treatment-related due to the absence of similar findings in the other animals. No treatment-related effects were observed on the male reproductive system, estrous cycle, number of implants, implantation index, pregnancy period, number of corpora lutea, live delivery index, the status of delivery or lactation, live offspring index, live birth index, viability index, or male-to-female ratio. Based on mortality and clinical findings associated with treatment and pregnancy-related stress at 300 mg/kg/day, the NOAEL for the fertility endpoint is 100 mg/kg/day. Based on the mortality of offspring at 300 mg/kg/day, the NOAEL for the developmental endpoint is 100 mg/kg/day (ECHA, 2018).

Therefore, the MOE can be calculated by dividing the NOAEL (in mg/

kg/day) for 3-ethylphenol by the total systemic exposure (in mg/kg/day) of 3-ethylphenol, 100/0.0008 or 125000.

In addition, the total systemic exposure to 3-ethylphenol (0.8 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

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

11.1.4. Skin sensitization

Based on existing data and the application of DST, *p*-ethylphenol does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. While the chemical structure of this material indicates that it would not be expected to react with skin proteins directly, its metabolite is expected to be reactive (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig Buehler test, *p*-ethylphenol did not present reactions indicative of sensitization (RIFM, 1980). Acting conservatively due to the insufficient data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for *p*-ethylphenol that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent the maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

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

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *p*-ethylphenol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for *p*-ethylphenol in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, *p*-ethylphenol does not 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 minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/22/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for *p*-ethylphenol 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 *p*-ethylphenol. Based on the Creme RIFM Model, the inhalation exposure is 0.00048 mg/day. This exposure is 2917 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Table 1
Maximum acceptable concentrations for *p*-ethylphenol that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	1.3×10^{-5}%
2	Products applied to the axillae	0.0015%	8.3×10^{-4}%
3	Products applied to the face using fingertips	0.029%	2.3×10^{-4}%
4	Fine fragrance products	0.027%	3.1×10^{-3}%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	8.1×10^{-4}%
6	Products with oral and lip exposure	0.016%	1.1×10^{-2}%
7	Products applied to the hair with some hand contact	0.056%	4.2×10^{-4}%
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	2.4×10^{-4}%
10	Household care products with mostly hand contact	0.19%	1.1×10^{-3}%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	2.7×10^{-2}%

Note.
[b]No reported use.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/13/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *p*-ethylphenol 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, *p*-ethylphenol 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 *p*-ethylphenol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), *p*-ethylphenol presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. No data available.

11.2.2.2. Ecotoxicity. No data available.

11.2.2.3. Other available data. *p*-Ethylphenol has been registered for REACH with the following additional data available at this time:

The ready biodegradability of the test material was evaluated using the headspace test according to the OECD 310 guidelines. Biodegradation of 87% was observed after 28 days (ECHA, 2018).

The acute fish (*Pimephales promelas*) toxicity test was conducted according to the OECD 203 guidelines under flow-through conditions. The 96-h LC50 value based on the mean measured concentration was reported to be 10.4 mg/L (ECHA, 2018).

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h effective concentration 50 (EC50) value based on nominal test concentration was reported to be 9 mg/L (95% CI: 6.2–12 mg/L) (ECHA, 2018).

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value based on nominal concentration was reported to be > 22 mg/L (ECHA, 2018).

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	2.58	2.58
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 0.05156 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/21/19.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	51.56			1000000	0.05156	

&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 09/22/20.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.111985.

Appendix

Read-across Justification

Methods

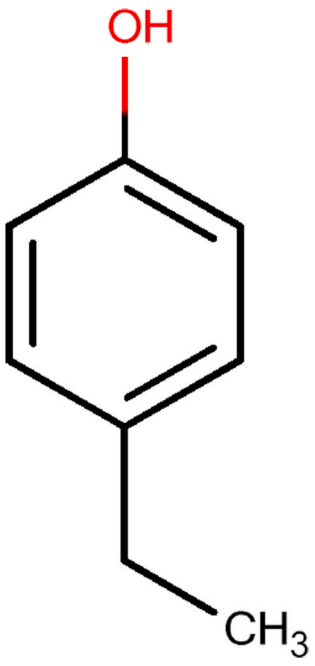
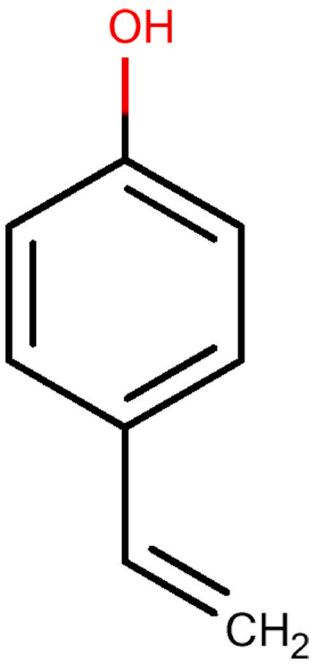
The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) 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 analog 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 analog were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Weight of evidence
Principal Name	*p*-Ethylphenol	*p*-Vinylphenol
CAS No.	123-07-9	2628-17-3
Structure		

(*continued on next page*)

(*continued*)

	Target Material	Weight of evidence
		
Similarity (Tanimoto Score)		0.67
Read-across Endpoint		• Genotoxicity
Molecular Formula	$C_8H_{10}O$	C_8H_8O
Molecular Weight	122.16	120.15
Melting Point (°C, EPI Suite)	45.0	73.5
Boiling Point (°C, EPI Suite)	217.90	209.22
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.960	1.867
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.58	2.41
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4900.0	3302.0
J_{max} (μg/cm^2/h, SAM)	439.1	253.7
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.83E-002	2.92E-002
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	• No alert found
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)**	• No alert found	• No alert found
Oncologic Classification	• Phenol Type Compounds	• Phenol Type Compounds
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 *p*-ethylphenol (CAS # 123-07-9). 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, *p*-vinylphenol (CAS # 2628-17-3) was identified as a read-across analog with sufficient data as WoE for toxicological evaluation.

Conclusions

- *p*-Vinylphenol (CAS # 2628-17-3) was used as a read-across analog for the target material *p*-ethylphenol (CAS # 123-07-9) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of phenols.
  - o The target material and the read-across analog share a phenol moiety.
  - o The key difference between the target material and the read-across analog is the target material has an ethyl group in the para position, whereas the read-across analog has a vinyl substitution in 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. 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 a 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 The target material has a DNA Binding (OECD QSAR) alert for Michael addition, which is not found for the read-across analog. Alkyl phenols can be oxidized by cytochrome P450 to a quinone methide followed by Michael addition, which has been suggested to be the primary route of DNA binding. Both the target material and read-across analog have an alert for phenols under the oncologic classification scheme. However, the data described in the genotoxicity section show that there is no concern for genotoxicity. Therefore, the predictions are superseded by 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.

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