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RIFM fragrance ingredient safety assessment, vanillyl ethyl ether, CAS Registry Number 13184-86-6

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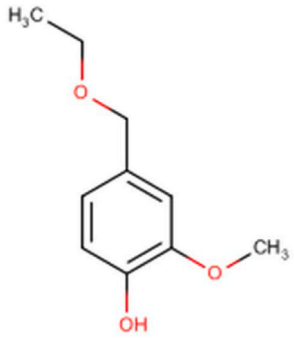


Name: Vanillyl ethyl ether
CAS Registry Number: 13184-86-6

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., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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
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

(*continued on next column*)

(*continued*)

(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.

Vanillyl ethyl ether was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog vanillyl butyl ether (CAS # 82654-98-6) show that vanillyl ethyl ether is not expected to be genotoxic. Data on read-across materials vanillyl butyl ether (CAS # 82654-98-6) and isoeugenol (CAS # 97-54-1) provide a calculated MOE >100 for the repeated dose toxicity and reproductive toxicity endpoints, respectively. Data from read-across analog vanillyl butyl ether (CAS # 82654-98-6) provided vanillyl ethyl ether a NESIL of 3500 □g/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; vanillyl ethyl ether is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material, and the exposure to vanillyl ethyl ether is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; vanillyl ethyl ether was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2000; RIFM, 2001c)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	RIFM (2001b)
Reproductive Toxicity: Developmental toxicity: NOAEL = 250 mg/kg/day. Fertility: NOAEL = 230 mg/kg/day.	(National Toxicology Program, 1999; National Toxicology Program, 2002)
Skin Sensitization: NESIL = 3500 □g/cm^2.	RIFM (2016a)
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: 5.4 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 536.9 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: 536.9 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.5369 □g/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Vanillyl ethyl ether
2. **CAS Registry Number:** 13184-86-6
3. **Synonyms:** 4-(Ethoxymethyl)-2-methoxyphenol; Ethyl 4-hydroxy-3-methoxybenzyl ether; Phenol, (4-ethoxymethyl)-2-methoxy-; VEE; Vanillyl ethyl ether
4. **Molecular Formula:** $C_{10}H_{14}O_3$
5. **Molecular Weight:** 182.21

6. **RIFM Number:** 7163
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 282.35 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 1.61 (EPI Suite)
4. **Melting Point**: 75.61 °C (EPI Suite)
5. **Water Solubility:** 2262 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000309 mm Hg at 20 °C (EPI Suite v4.0), 0.000596 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. <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 Toothpaste:** 0.000006% (RIFM, 2017b)

(No reported use in hydroalcoholics).

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2017b)
3. **Total Systemic Exposure**:** 0.0000001 mg/kg/day (RIFM, 2017b)

*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 v3.1	OECD QSAR Toolbox v4.2
III*	II	II

*See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** Vanillyl butyl ether (CAS # 82654-98-6)
   b. **Repeated Dose Toxicity:** Vanillyl butyl ether (CAS # 82654-98-6)
   c. **Reproductive Toxicity:** Isoeugenol (CAS # 97-54-1)
   d. **Skin Sensitization:** Vanillyl butyl ether (CAS # 82654-98-6)
   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

Vanillyl ethyl ether is not reported to occur in foods by the VCF*.

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

9. REACH dossier

Pre-registered for 2013; no dossier available as of 03/10/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for vanillyl ethyl ether 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)	0.27
2	Products applied to the axillae	0.080
3	Products applied to the face/body using fingertips	1.6
4	Products related to fine fragrances	1.5
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.38
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.38
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.38
5D	Baby cream, oil, talc	0.13
6	Products with oral and lip exposure	0.88
7	Products applied to the hair with some hand contact	3.1
8	Products with significant ano-genital exposure (tampon)	0.13
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	11
10B	Aerosol air freshener	11
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.13
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 vanillyl ethyl ether, the basis was the reference dose of 2 mg/kg/day, a predicted

skin absorption value of 80%, and a skin sensitization NESIL of 3500 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 v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, vanillyl ethyl ether does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of vanillyl ethyl ether; however, read-across can be made to vanillyl butyl ether (CAS # 82654-98-6; see Section VI).

The mutagenic activity of vanillyl butyl ether has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with vanillyl butyl ether in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2000). Under the conditions of the study, vanillyl butyl ether was not mutagenic in the Ames test, and this can be extended to vanillyl ethyl ether.

The clastogenic activity of vanillyl butyl ether 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 olive oil orally (gavage) to groups of male and female Crj:CD-1 mice. Doses of 500, 1000, or 2000 mg/kg were administered. Mice from each dose level were euthanized at 24 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 (RIFM, 2001c). Under the conditions of the study, vanillyl butyl ether was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to vanillyl ethyl ether.

Based on the data available, vanillyl butyl ether does not present a concern for genotoxic potential, and this can be extended to vanillyl ethyl ether.

Additional References: RIFM, 1989; RIFM, 1999b.

Literature Search and Risk Assessment Completed On: 12/17/20.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for vanillyl ethyl ether 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 methyl vanillyl ether. Read-across material vanillyl butyl ether (CAS # 82654-98-6; see Section VI) has sufficient repeated dose toxicity data. There are sufficient data on vanillyl butyl ether to support the repeated dose toxicity endpoint. In a subchronic OECD 407 and GLP-compliant study, 5 Wistar rats/sex/dose were administered the treatment material orally (gavage) at doses of 0, 35, 150, and 600 mg/kg/day for 28 days. No treatment-related mortality and adverse effects were reported in any dose group. Microscopic findings in the high-dose group revealed minimal to slight degrees of forestomach squamous hyperplasia (2M, 1F) and minimal to slight glandular inflammation (3M, 1F). However, these findings were not considered to be of concern to human health. Thus, based on the absence of any treatment-related adverse effects, the NOAEL for repeated dose toxicity was determined to be at 600 mg/kg/day (RIFM, 2001b).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day OECD 407 studies (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 600/3 or 200 mg/kg/day.

Therefore, the MOE can be calculated by dividing the NOAEL for vanillyl butyl ether in mg/kg/day by the total systemic exposure in mg/kg/day to vanillyl ethyl ether, 200/0.0000001 or 2000000000.

In addition, the total systemic to vanillyl ethyl ether (0.0001 μg/kg/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.

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 reference dose of 2 mg/kg/day.

11.1.2.1.1. Derivation of reference dose (RfD). 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 reference dose for vanillyl ethyl ether was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 200 mg/kg/day by the uncertainty factor, 100 = 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.

Additional References: JECFA, 2002; RIFM, 2002; RIFM, 2005; RIFM, 2008.

Literature Search and Risk Assessment Completed On: 12/15/20.

11.1.3. Reproductive toxicity

The MOE for vanillyl ethyl ether is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on vanillyl ethyl ether. Read-across material isoeugenol (CAS # 97-54-1; see Section VI) has sufficient 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/

Table 1
Data Summary for vanillyl butyl ether as read-across material for vanillyl ethyl ether.

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
3645	Weak	3543	NA	NA	3500

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.

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 dams in the 500 and 1000 mg/kg/day dose groups. A statistically significant decrease in body weight and a statistically significant increase in the incidence of non-ossified sternebrae were reported in pups of the 1000 mg/kg/day dose group. 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 (National Toxicology Program, 1999; George et al., 2001).

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

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

The vanillyl ethyl ether MOE for the developmental toxicity endpoint can be calculated by dividing the isoeugenol NOAEL in mg/kg/day by the total systemic exposure to vanillyl ethyl ether, 250/0.0000001 or 2500000000.

The vanillyl ethyl ether MOE for the fertility endpoint can be calculated by dividing the isoeugenol NOAEL in mg/kg/day by the total systemic exposure to vanillyl ethyl ether, 230/0.0000001 or 2300000000.

In addition, the total systemic exposure to vanillyl ethyl ether (0.0001 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/15/20.

11.1.4. Skin sensitization

Based on the read-across material vanillyl butyl ether (CAS # 82654-98-6), vanillyl ethyl ether is considered a skin sensitizer with a defined NESIL of 3500 μg/cm^2.

11.1.4.1. Risk assessment. No data on skin sensitization studies are available for vanillyl ethyl ether. Based on the read-across material vanillyl butyl ether (CAS # 82654-98-6; see Section VI), vanillyl ethyl ether 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 vanillyl butyl ether was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, and human cell line activation test (h-CLAT) (RIFM, 2016b; RIFM, 2016c; RIFM, 2018). In a murine local lymph node assay (LLNA), read-across material vanillyl butyl ether was found to be sensitizing with an EC3 value of 14.58% (3645 μg/cm^2) (RIFM, 2006). In 2 guinea pig maximization tests, read-across material vanillyl butyl ether presented reactions indicative of sensitization at 10% and 100% (RIFM, 1999a; RIFM, 2001a). In a Confirmation of No Induction in Humans test (CNIH) with 3% (3543 μg/cm^2) read-across material vanillyl butyl ether in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 104 volunteers (RIFM, 2016a).

Based on the available data on read-across material vanillyl butyl ether, summarized in Table 1, vanillyl ethyl ether is considered to be a weak skin sensitizer with a defined No Expected Sensitization Induction Level (NESIL) of 3500 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 reference dose of 2 mg/kg/day).

Additional References: RIFM, 2017a; ECHA, 2011.

Literature Search and Risk Assessment Completed On: 12/18/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, vanillyl ethyl ether 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 vanillyl ethyl ether in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	536.9			1000000	0.5369	

concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, vanillyl ethyl ether does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/11/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for vanillyl ethyl ether 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 vanillyl ethyl ether. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 4700 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: 12/16/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of vanillyl ethyl ether 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, vanillyl ethyl ether 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 vanillyl ethyl ether 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).

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

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.3. Other available data. Vanillyl ethyl ether has been pre-registered for REACH with no additional data available at this time.

11.2.2. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.61	1.61
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	NA
Risk Characterization: PEC/PNEC	**<1**	**NA**

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

The RIFM PNEC is 0.5369 μg/L. The revised PEC/PNECs for EU and NA (No VoU) 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: 12/16/20.

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 03/10/21.

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.2021.112477.

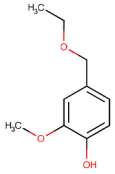
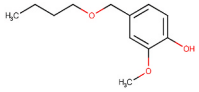
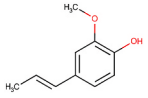
Appendix

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, 2017).

- 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
Principal Name	Vanillyl ethyl ether	Vanillyl butyl ether	Isoeugenol
CAS No.	13184-86-6	82654-98-6	97-54-1
Structure			
Similarity (Tanimoto Score)		0.87	0.54
Read-across Endpoint		• Genotoxicity • Repeated Dose Toxicity • Skin Sensitization	• Reproductive Toxicity
Molecular Formula	$C_{10}H_{14}O_3$	$C_{12}H_{18}O_3$	$C_{10}H_{12}O_2$
Molecular Weight	182.21	210.27	164.20
Melting Point (°C, EPI Suite)	75.61	94.67	33.50
Boiling Point (°C, EPI Suite)	282.35	312.01	266.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.95E-02	9.23E-03	1.80E+00
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	1.61	2.59	3.04
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2262	236.4	810

(continued on next page)

(*continued*)

	Target Material	Read-across Material	Read-across Material
J_{max} (μg/cm^2/h, SAM)	97.437	47.714	79.642
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.77E-05	1.01E-04	2.71E-03
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 ≫ 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	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Moderate binder, OH group		• Weak binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (moderate reliability)		• Non-toxicant (low reliability)
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			
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

Summary

There are insufficient toxicity data on vanillyl ethyl ether (CAS # 13184-86-6). 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, vanillyl butyl ether (CAS # 82654-98-6) and isoeugenol (CAS # 97-54-1) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Vanillyl butyl ether (CAS # 82654-98-6) was used as a read-across analog for the target material vanillyl ethyl ether (CAS # 13184-86-6) for the skin sensitization, genotoxicity, and repeated dose toxicity endpoints.

  The target material and the read-across analog are structurally similar and are 4-substituted-2-methoxyphenols, which would yield catechols upon metabolism.

  The target material and the read-across analog share 4-substituted-2-methoxyphenol structures.

  The key difference between the target material and the read-across analog is that the target material has an ethoxymethyl substitution on the 4 position, whereas the read-across analog has a butoxymethyl substitution on the same position. This structural difference is toxicologically insignificant.

  Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

  The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.

  According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.

  The target material and the read-across analog have an alert for Michael addition, P450-mediated activation of quinones or quinone-type chemicals, and phenol-type compounds. This alert is due to the presence of the 4-position alkyl group to OH on the aromatic ring. The data described in the genotoxicity section for the read-across analog confirm that the substance does not pose a concern for genetic toxicity. Therefore, based on the structural similarity and the data, the alert is superseded.

  The target material and a read-across analog also have an alert for an H-acceptor-path3-H-acceptor. They also have an alert for phenol-type compounds. This is due to the fact that they both have 1-hydroxy and 2-methoxy substitutions on the aromatic ring. These alerts confirm the comparability of the reactivity between the target material and the read-across analog. The data described in the genotoxicity section for the

read-across analog confirm that the substance does not pose a concern for genetic toxicity. Therefore, based on the structural similarity and the data, the alert is superseded.

The target material has an alert for methoxamine toxicity for repeat dose by HESS categorization. This is due to the fact that the target material shares more than 50% structural similarity with the chemical methoxamine, which is a known renal toxicant. Although the target material shares more than 50% structural similarity with methoxamine, the reactive moiety of methoxamine NC(C)C(O) is not present on the target material. Therefore, this alert is out of domain for the target. Also, the data described in the genotoxicity section for the read-across analog confirms that the substance does not pose a concern for genetic toxicity. Therefore, based on the structural similarity and the data, the alert is superseded.

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.

- Isoeugenol (CAS # 97-54-1) was used as a read-across analog for the target material vanillyl ethyl ether (CAS # 13184-86-6) for the reproductive toxicity endpoint.

  The target material and the read-across analog are structurally similar 4-substituted-2-methoxyphenols, which would yield catechols upon metabolism.

  The target material and the read-across analog share a 4-substituted-2-methoxyphenol structure.

  The key difference between the target material and the read-across analog is that the target material has an ethoxymethyl substitution on the 4 position, whereas the read-across analog has a 2-ethene substitution on the same position. This structural difference is toxicologically insignificant.

  Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

  The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.

  According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.

  The target material and the read-across analog have an alert for ER binding, and they are predicted to be weak binders with the OH group. This is because of the presence of OH on the aromatic ring. The data described in the repeated dose toxicity section above confirm that the read-across analog has an adequate MOE under the current level of use. The predictions are superseded by the data.

  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.

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.

Q1. 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
Q7. Heterocyclic? No
Q16. Common terpene (see Cramer et al., 1978 for 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? Yes
Q33. Has 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 III (Class High)

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