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Short Review

RIFM fragrance ingredient safety assessment, 2-ethoxy-4-[(1-methylethoxy)methyl] phenol, CAS Registry number 96840-56-1

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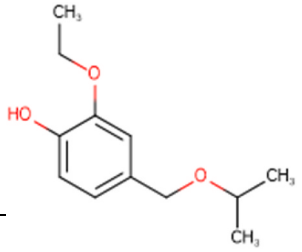

Name: 2-Ethoxy-4-[(1-methylethoxy) methyl] phenol
CAS Registry Number: 96840-56-1

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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017, 2024) 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
LOEL - Lowest Observed 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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
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

(*continued on next column*)

(*continued*)

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-[(1-methylethoxy)methyl] phenol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-ethoxy-4-(methoxymethyl)phenol (CAS # 5595-79-9) show that 2-ethoxy-4-[(1-methylethoxy)methyl] phenol is not expected to be genotoxic. Data on read-across analog vanillyl butyl ether (CAS # 82654-98-6) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. These data were extrapolated to derive a point of departure (PoD) for the reproductive toxicity endpoint. Data from read-across analog 2-methoxy-4-propylphenol (CAS # 2785-87-7) provided 2-ethoxy-4-[(1-methylethoxy)methyl] phenol a No Expected Sensitization Induction Level (NESIL) of 1700 μg/cm^2 for the skin sensitization endpoint. The photoirritation endpoint was evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 2-ethoxy-4-[(1-methylethoxy)methyl] phenol is not photoirritating. The photoallergenicity endpoint was evaluated based on UV/Vis spectra; 2-ethoxy-4-[(1-methylethoxy)methyl] phenol is not expected to be 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-[(1-methylethoxy)methyl] phenol is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 2-ethoxy-4-[(1-methylethoxy)methyl] phenol 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 (VoU) 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.	(RIFM, 2002a; RIFM, 2002b; RIFM, 2003)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	RIFM (2001)
Reproductive Toxicity: NOAEL = 66.67 mg/kg/day.	RIFM (2001)
Skin Sensitization: NESIL = 1700 μg/cm^2.	(RIFM, 2015)
Photoirritation/Photoallergenicity: Not photoirritating/not expected to be photoallergenic.	(UV/Vis Spectra, RIFM Database; RIFM, 2016)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 2.7 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 21.3 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 104 mg/L (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 (Salvito et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 104 mg/L (Salvito et al., 2002)

RIFM PNEC is: 0.104 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not Applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** 2-Ethoxy-4-[(1-methylethoxy)methyl] phenol
2. **CAS Registry Number:** 96840-56-1
3. **Synonyms:** Propyl diantilis; Phenol, 2-ethoxy-4-[(1-methylethoxy) methyl]-; 2-Ethoxy-4-[(1-methylethoxy)methyl] phenol
4. **Molecular Formula:** $C_{12}H_{18}O_3$
5. **Molecular Weight:** 210.27 g/mol
6. **RIFM Number:** 7145
7. **Stereochemistry:** No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 303.45 °C (EPI Suite v4.11)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 2.52 (EPI Suite v4.11)
4. **Melting Point**: 86.33 °C (EPI Suite v4.11)
5. **Water Solubility:** 273.2 mg/L at 25 °C (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000138 mm Hg (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 700 nm under acidic conditions and minor absorbance between 290 and 700 nm under biologically relevant neutral conditions; molar absorption coefficients (0 and 808 L mol^{-1} • cm^{-1} for acidic and neutral conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1}). Significant absorbance between 290 and 700 nm under basic conditions, with a peak at 290 nm and returning to baseline by 400 nm. The molar absorbance coefficient (1792 L mol^{-1} • cm^{-1} for basic condition) is above the benchmark (1000 L mol^{-1} • cm^{-1}).
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2019)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.074% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0036 mg/kg/day or 0.26 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0039 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 et al., 2015, 2017, 2024).

**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 et al., 2015, 2017, 2024).

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 v4.5 (OECD, 2021b)
III	I	II

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** 2-Ethoxy-4-(methoxymethyl)phenol (CAS # 5595-79-9)
   b. **Repeated Dose Toxicity:** Vanillyl butyl ether (CAS # 82654-98-6)
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-Methoxy-4-propylphenol (CAS # 2785-87-7)
   e. **Photoirritation/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

2-Ethoxy-4-[(1-methylethoxy)methyl] phenol 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

2-Ethoxy-4-[(1-methylethoxy)methyl] phenol has not been pre-registered; no dossier is available as of 100424.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-ethoxy-4-[(1-methylethoxy)methyl] phenol 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)	0.024
2	Products applied to the axillae	0.039
3	Products applied to the face/body using fingertips	0.024
4	Products related to fine fragrances	0.73
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.18
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.049
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.049
5D	Baby cream, oil, talc	0.016
6	Products with oral and lip exposure [Note: Can have rinse-off levels, which would be the NOAEL]	0.024

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(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
7	Products applied to the hair with some hand contact	0.073
8	Products with significant ano-genital exposure (tampon)	0.016
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.29
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.024
10B	Aerosol air freshener	5.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.016
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 2-ethoxy-4-[(1-methylethoxy)methyl] phenol, the basis was the reference dose of 0.67 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 1700 μg/cm^2.

As a conservative approach, we assumed that 100% of the material exposed via the skin is bioavailable (see Section V), thereby deriving the most stringent MOE. Since the MOE is > 100 (see the repeated dose and reproductive toxicity sections), we then refined the exposure to 40% using an *in silico* Skin Absorption Model (SAM) to determine the Maximum Allowable Concentrations for each category listed in Section X.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA/Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.4.1.

11. Summary

11.1. Human Health Endpoint Summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-ethoxy-4-[(1-methylethoxy)methyl] phenol does not present a concern for genotoxicity.

11.1.1.1. Risk Assessment. 2-Ethoxy-4-[(1-methylethoxy)methyl] phenol was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) with and without metabolic activation, positive for genotoxicity without metabolic activation, and negative for genotoxicity with metabolic activation (RIFM, 2013). These positive results were observed at cytotoxic concentrations that were within the acceptable range for the BlueScreen assay (positive: <80% relative cell density). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of 2-ethoxy-4-[(1-methylethoxy)methyl] phenol; however, read-across can be made to 2-ethoxy-4-(methoxymethyl)phenol (CAS # 5595-79-9; see Section VI).

The mutagenic activity of 2-ethoxy-4-(methoxymethyl)phenol 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 2-ethoxy-4-(methoxymethyl)phenol 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, 2002a). Under the conditions of the study, 2-ethoxy-4-(methoxymethyl)phenol was not mutagenic in the Ames test, and this can be extended to 2-ethoxy-4-[(1-methylethoxy)methyl] phenol.

The clastogenicity of 2-ethoxy-4-(methoxymethyl)phenol 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 2-ethoxy-4-(methoxymethyl)phenol in ethanol at concentrations up to 1830 μg/mL in the dose range finding study; the main study was conducted at concentrations up to 1830 μg/mL in the presence and absence of metabolic activation. Statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed at 1500 μg/mL without metabolic activation and at 1830 μg/mL with metabolic activation (RIFM, 2002b). At 1500 μg/mL, the aberration rate (8.0%) exceeded the historical control range (0.0%–4.0%), and the number of cells carrying exchanges (5.3%) was increased compared to the solvent control (1.0%). At 1830 μg/mL, the aberration rate (19.0%) exceeded the solvent control (1.5%), and the number of cells carrying exchanges (6.5%) was increased compared to the solvent control (1.0%). Under the conditions of the study, 2-ethoxy-4-(methoxymethyl)phenol was considered to be clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to 2-ethoxy-4-[(1-methylethoxy)methyl] phenol.

To verify the results observed in the *in vitro* chromosome aberration study, the clastogenic activity of 2-ethoxy-4-(methoxymethyl)phenol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral administration to groups of male and female NMRI mice. Single doses of 450, 900, and 1800 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2003). Under the conditions of the study, 2-ethoxy-4-(methoxymethyl) phenol was considered not to be clastogenic in the *in vivo* micronucleus test, and this can be extended to 2-ethoxy-4-[(1-methylethoxy)methyl] phenol.

Based on the data available, 2-ethoxy-4-(methoxymethyl)phenol does not present a concern for genotoxic potential, and this can be extended to 2-ethoxy-4-[(1-methylethoxy)methyl] phenol.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/01/23.

11.1.2. Repeated Dose Toxicity

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

11.1.2.1. Risk Assessment. There are no repeated dose data on 2-ethoxy-4-[(1-methylethoxy)methyl] phenol. The read-across material vanillyl butyl ether (CAS # 82654-98-6; See Section VI) has sufficient repeated dose toxicity data.

In a subchronic OECD 407 and GLP-compliant study, 5 Wistar rats/sex/dose were orally administered the test material at doses of 0, 35, 150, and 600 mg/kg/day for 28 days. No treatment-related mortality or adverse effects were reported in any dose group. Microscopic findings in the high-dose group revealed a minimal to slight degree of forestomach squamous hyperplasia (2 M, 1F) and minimal to slight glandular inflammation (3 M, 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, 2001).

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 by the total systemic exposure, 200/0.0039 or 51282.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/23/23.

11.1.3. Reproductive Toxicity

The MOE 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 2-ethoxy-4-[(1-methylethoxy)methyl] phenol or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-ethoxy-4-[(1-methylethoxy)methyl] phenol (3.9 μg/kg/day) is above 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.

As the repeated dose toxicity data on read-across material vanillyl butyl ether (CAS # 82654-98-6; see Section VI) are sufficient to draw a NOAEL (using a subchronic study), the repeated dose toxicity PoD can be adjusted to a reproductive toxicity PoD using an uncertainty factor (UF) and a Developmental and Reproductive Toxicity (DART) factor (Blackburn et al., 2015; Wu et al., 2013).

In a subchronic OECD 407 and GLP-compliant study, 5 Wistar rats/sex/dose were orally administered the test material at doses of 0, 35, 150, and 600 mg/kg/day for 28 days. No treatment-related mortality or adverse effects were reported in any dose group. Microscopic findings in the high-dose group revealed a minimal to slight degree of forestomach squamous hyperplasia (2 M, 1F) and minimal to slight glandular inflammation (3 M, 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, 2001).

Because the repeated dose toxicity data on read-across vanillyl butyl ether are sufficient to draw a NOAEL (sub-acute study), this PoD can be adjusted to a reproductive toxicity PoD using 2 UFs: (1) a duration factor of 3x to convert sub-acute to subchronic, and (2) a DART factor.

To determine the value of the DART factor, the structure of vanillyl butyl ether was analyzed using P&G DART Automated Tree (Version 1.7) to investigate its potential to cause DART reactivity or toxicity. The structure was first compared with a library of structures known to be negative for DART effects, but no matches were found in this library. The structure of the material was then compared to all structures in the DART Precedent database. The DART Precedent database includes all possible chemical structures enumerated from the substructures and rules for allowable substituents for all 25 subcategories of DART toxicants (Blackburn et al., 2015; Wu et al., 2013). There were no matches with a sufficient mapping score found in this library. The structure was next compared to all structures in the DART Substructure/Scaffold database to determine the degree of 'scaffold' match, and any/all overlaps of portions of the material structure with the scaffolds in the database are reported. The DART DT scaffold database includes all the 'scaffold' or core structures derived from the substructures defined for each of the 25 categories of DART toxicants (Blackburn et al., 2015; Wu et al., 2013). A scaffold match was detected with subcategory 2b-3-2 in that the structure is within the unsaturated 4-alkylphenol Derivatives. An ethoxy phenol is missing the R1 groups required for toxicity. In the presence of matches to a scaffold match, a database UF of 3X is applied.

The cumulative product of the duration and DART UFs is $3 \times 3 = 9$.

Thus, the reproductive toxicity NOAEL for the developmental toxicity and fertility endpoints can be calculated by dividing the repeated dose toxicity NOAEL by the cumulative product of the UFs, $600/9 = 66.67$ mg/kg/day.

Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 66.67/0.0039 or 17094.

11.1.3.1.1. Derivation of Reference Dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and an RfD of 0.67 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for inter-species (10 ×) and intraspecies (10 ×) differences. The RfD for 2-ethoxy-4-[(1-methylethoxy)methyl] phenol was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 66.67 mg/kg/day by the uncertainty factor, 100 = 0.67 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/23/23.

11.1.4. Skin Sensitization

Based on the existing data on the read-across material 2-methoxy-4-propylphenol, 2-ethoxy-4-[(1-methylethoxy)methyl] phenol is a skin sensitizer with a defined NESIL of 1700 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

11.1.4.1. Risk Assessment. Limited skin sensitization data are available for 2-ethoxy-4-[(1-methylethoxy)methyl] phenol. Therefore, 2-methoxy-4-propylphenol (CAS # 2785-87-7; see Section VI) was used for the risk assessment of 2-ethoxy-4-[(1-methylethoxy)methyl] phenol. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, 2-ethoxy-4-[(1-methylethoxy)methyl] phenol is a skin sensitizer. 2-ethoxy-4-[(1-methylethoxy)methyl] phenol and read-across material 2-methoxy-4-propylphenol are predicted *in silico* to be non-reactive with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Read-across material 2-methoxy-4-propylphenol was found to be borderline in an *in vitro* direct peptide reactivity assay (DPRA) and positive in a KeratinoSens, a human cell line activation test (h-CLAT), and a U937-CD86 test (Natsch, 2013; Emter et al., 2010; Piroird et al., 2015). The results were evaluated following the OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a), and based on the 2 out of 3 Defined Approach, 2-methoxy-4-propylphenol is a sensitizer. In a murine local lymph node assay (LLNA), read-across material 2-methoxy-4-propylphenol was found to be sensitizing with an EC3 value of 6.8% (1700 μg/cm^2) (ECHA, 2016). In guinea pig maximization tests, read-across material 2-methoxy-4-propylphenol reactions indicative of sensitization were observed (RIFM, 1989; RIFM, 1988; ECHA, 2016). In a human maximization test, no skin sensitization reactions were observed when read-across material 2-methoxy-4-propylphenol was tested at 5520 μg/cm^2 (RIFM, 1977). In a Confirmation of No Induction in Humans test (CNIH) with 2000 μg/cm^2 of 2-ethoxy-4-[(1-methylethoxy)methyl] phenol in an unknown vehicle, reactions indicative of sensitization were observed in 1/51 volunteers (RIFM, 1986). Similarly, in a CNIH with 5000 μg/cm^2 of 2-ethoxy-4-[(1-methylethoxy)methyl] phenol in dimethyl phthalate, reactions indicative of sensitization were observed in 1/48 volunteers (RIFM, 1985). The 2 CNIHs are inconclusive because the purity of the materials tested over 40 years ago is unknown; additionally, the first study used an unknown vehicle, while the second one used a non-standard vehicle. Additionally, in a CNIH with 1771 μg/cm^2 of read-across material 2-methoxy-4-propylphenol in 1:3 ethanol:diethyl phthalate, no

Table 1
Summary of existing data on 2-methoxy-4-propylphenol as a read-across for 2-ethoxy-4-[(1-methylethoxy)methyl] phenol.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL (induction) µg/cm²	WoE NESIL[2] µg/cm²	LLNA[3] Weighted Mean EC3 Value µg/cm²	GPMT[4]	Buehler
Moderate	1771	5520	N/A	1700	1700 (6.8%)	Positive	N/A
	In vitro Data[5]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Inconclusive	Positive	Positive		No alert found	Michael addition	Schiff base formation; Michael addition

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; EC3 = concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = Not Available.
[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
[2]WoE NESIL limited to 2 significant figures.
[3]Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).
Studies conducted according to the OECD TG 406 are included in the table.
[5]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

reactions indicative of sensitization were observed in any of the 107 volunteers (RIFM, 2015).

Based on the weight of evidence (WoE) from structural analysis, *in vitro* studies, animal studies, and human studies on the read-across material and the target material, 2-ethoxy-4-[(1-methylethoxy)methyl] phenol is a sensitizer with a WoE NESIL of 1700 µg/cm^2 (Table 1). 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. (2020) and an RfD of 0.67 mg/kg/day.

Additional References: Itoh (1982); Natsch (2007); Natsch (2008).

Literature Search and Risk Assessment Completed On: 01/25/24.

11.1.5. Photoirritation/Photoallergenicity

Based on the available UV/Vis spectra and *in vitro* study data, 2-ethoxy-4-[(1-methylethoxy)methyl] phenol would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, 2-ethoxy-4-[(1-methylethoxy)methyl] phenol would not be expected to present a concern for photoallergy.

11.1.5.1. Risk Assessment. UV/Vis absorption spectra indicate no absorption and minor absorption between 290 and 700 nm under the acidic and biologically relevant neutral conditions, respectively. The corresponding molar absorption coefficients (0 and 808 L mol^{-1} • cm^{-1}) are below the benchmark of concern for photoirritating and photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009). Molar absorbance under basic conditions was above the benchmark of concern, but in this assay, basic conditions are defined as pH 10 or greater and thus do not represent a biologically relevant condition for exposure via the dermal route. In an *in vitro* 3T3-Neutral Red uptake phototoxicity assay (OECD TG 432), 2-ethoxy-4-[(1-methylethoxy)methyl] phenol was not predicted to be photoirritating (RIFM, 2016). Based on the available UV/Vis spectra and *in vitro* data, 2-Ethoxy-4-[(1-methylethoxy)methyl] phenol would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, 2-ethoxy-4-[(1-methylethoxy)methyl] phenol would not be expected to present a concern for photoallergy.

11.1.5.2. UV Spectra Analysis. UV/Vis absorption spectra (OECD TG 101) were generated for 2-Ethoxy-4-[(1-methylethoxy)methyl] phenol. The spectra indicate no absorbance and minor absorbance in the range of 290–700 nm under the acidic and biologically relevant neutral condition. The molar absorption coefficients (0 and 808 L mol^{-1} • cm^{-1}) are below the benchmark of concern for photoirritating and photoallergic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009). Under basic conditions, the molar absorption coefficient (1795 L mol^{-1} • cm^{-1}) was above the benchmark.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/21/23.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-Ethoxy-4-[(1-methylethoxy)methyl] phenol 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-[(1-methylethoxy)methyl] phenol. Based on the Creme RIFM Model, the inhalation exposure is 0.26 mg/day. This exposure is 1.8 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: 08/22/23.

11.2. Environmental Endpoint Summary

11.2.1. Screening-Level Assessment

A screening-level risk assessment of 2-ethoxy-4-[(1-methylethoxy) methyl] phenol 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 UF 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 UF 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 UFs. 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 VoU 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-[(1-methylethoxy) methyl] phenol 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 2-ethoxy-4-[(1-methylethoxy)methyl] phenol as possibly being 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 VoU (IFRA, 2019), 2-ethoxy-4-[(1-methylethoxy)methyl] phenol does not present a 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.

11.2.1.2.3. Other Available Data. No additional data available.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>104</u>			1000000	0.104	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.51	2.51
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU 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 0.104 μg/L. The revised PEC/PNECs for EU and

NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 08/15/23.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 10/04/24.

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.2024.115115.

Appendix

Read-across Justification:

Methods

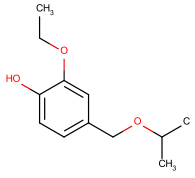
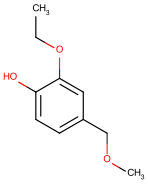
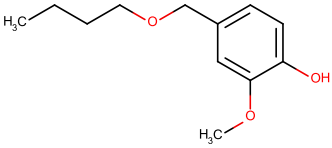
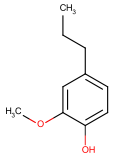
The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (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 v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	2-Ethoxy-4-[(1-methylethoxy) methyl] phenol	2-Ethoxy-4-(methoxymethyl) phenol	Vanillyl butyl ether	2-Methoxy-4-propylphenol
CAS No.	96840-56-1	5595-79-9	82654-98-6	2785-87-7

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
Structure				
Similarity (Tanimoto Score)		0.89	0.76	0.47
SMILES	CCOc1cc(COC(C)C)ccc1O	CCOc1cc(COC)ccc1O	CCCCOCc1ccc(O)c(OC)c1	CCCc1ccc(O)c(OC)c1
Endpoint		Genotoxicity	Repeated dose toxicity	Skin sensitization
Molecular Formula	$C_{12}H_{18}O_3$	$C_{10}H_{14}O_3$	$C_{12}H_{18}O_3$	$C_{10}H_{14}O_2$
Molecular Weight	210.273	182.219	210.273	166.22
Melting Point (°C, EPI Suite)	86.33	75.61	94.67	61.64
Boiling Point (°C, EPI Suite)	303.45	282.35	312.01	265.51
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.84E-02	7.95E-02	9.23E-03	2.84E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.73E+02	2.26E+03	2.36E+02	2.28E+02
Log KOW	2.52	1.61	2.59	2.87
J_{max} (μg/cm^2/h, SAM)	3.05	11.45	2.96	12.17
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.01E-04	5.77E-05	1.01E-04	6.54E-03
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found		
DNA Binding (OECD QSAR Toolbox v4.5)	No alert found	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)**	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	
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)	No skin sensitization reactivity domain alerts identified			Alert for Michael Acceptor identified
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on 2-ethoxy-4-[(1-methylethoxy)methyl] phenol (CAS # 96840-56-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 2-ethoxy-4-(methoxymethyl)phenol (CAS # 5595-79-9), vanillyl butyl ether (CAS # 82654-98-6), and 2-methoxy-4-propylphenol (CAS # 2785-87-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 2-Ethoxy-4-(methoxymethyl)phenol (CAS # 5595-79-9) was used as a read-across analog for the target material, 2-ethoxy-4-[(1-methylethoxy) methyl] phenol (CAS # 96840-56-1), for the genotoxicity endpoint.
  - o The target material and the read-across analog are both phenols with ether functionality.
  - o The key difference between the target material and the read-across analog is that the target material contains a branched ether, whereas the read-across analog does not. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - o The 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.
- Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
- According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- Both the target material and read-across analog contain an *in silico* alert for H-acceptor-path3-H-acceptor (genotoxicity). The data from the genotoxicity section confirms that the read-across analog is not genotoxic. Therefore, based on the structural similarity of the target material and read-across analog and the data on the read-across analog, 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.

- Vanillyl butyl ether (CAS # 82654-98-6) was used as a read-across analog for the target material, 2-ethoxy-4-[(1-methylethoxy)methyl] phenol (CAS # 96840-56-1), for the repeated dose toxicity endpoint.
  - The target material and the read-across analog are both phenols with ether functionality.
  - The key difference between the target material and the read-across analog is that the read-across analog contains a longer carbon chain for the ether functionality compared to the target material. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - The 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 v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Neither the target material nor the read-across analog contains *in silico* alerts for repeated dose toxicity. The data from the repeated dose toxicity section confirms that the MOE for the target material is adequate under the current usage. Therefore, *in silico* alerts are consistent with 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.
- 2-Methoxy-4-propylphenol (CAS # 2785-87-7) was used as a read-across analog for the target material, 2-ethoxy-4-[(1-methylethoxy)methyl] phenol (CAS # 96840-56-1), for the skin sensitization endpoint.
  - The target material and the read-across analog are both phenols with ether functionality.
  - The key difference between the target material and the read-across analog is that the read-across analog does not contain an isolated ether linkage in the hydrocarbon chain para to the hydroxy group, whereas the target material does. Additionally, the target has an ethoxy group ortho to the hydroxy group, whereas the read-across analog has a methoxy ortho to the hydroxy group. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - The 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.
  - Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The read-across analog contains an alert for a Michael acceptor, whereas the target material does not for Skin Sensitization Reactivity Domains. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. The data from the skin sensitization section confirms that the read-across analog is a skin sensitizer. Therefore, *in silico* alerts are consistent with 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 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).

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, 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? No.
Q17. Readily hydrolyzed to a common terpene? No.
Q18. One of the list (see explanation)? 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? 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).

References

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