Food and Chemical Toxicology 183 (2024) 114514

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, isoeugenyl benzyl ether, CAS Registry Number 120-11-6

A.M. Api [a], A. Bartlett [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], A. Bryant-Freidrich [d], G.A. Burton Jr. [e], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [f], W. Dekant [g], C. Deodhar [a], K. Farrell [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], H. Moustakas [a], J. Muldoon [a], T.M. Penning [i], G. Ritacco [a], N. Sadekar [a], I. Schember [a], T.W. Schultz [j], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, Pharmaceutical Sciences, Wayne State University, 42 W. Warren Ave., Detroit, MI, 48202, USA*
[e] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[f] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. Dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

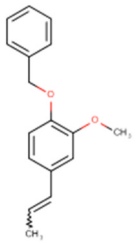
ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2024.114514
Received 30 January 2024; Received in revised form 8 February 2024; Accepted 11 February 2024
Available online 17 February 2024

Version: 012324. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: Isoeugenyl benzyl ether
CAS Registry Number: 120-11-6

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
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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey 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; 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
ISS - Instituto Superiore di Sanita (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
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.

(*continued on next page*)

(*continued*)

Isoeugenyl benzyl ether was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog isoeugenyl methyl ether (CAS # 93-16-3) show that isoeugenyl benzyl ether is not expected to be genotoxic. Data on isoeugenyl benzyl ether provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to isoeugenyl benzyl ether is below the TTC (0.0015 mg/kg/day and 0.47 mg/day, respectively). Data from read-across analog isoeugenyl methyl ether (CAS # 93-16-3) provided isoeugenyl benzyl ether a No Expected Sensitization Induction Level (NESIL) of 9400 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; isoeugenyl benzyl ether is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; isoeugenyl benzyl ether 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. (ECHA, 2019; RIFM, 2015)
Repeated Dose Toxicity: NOEL = 80 mg/kg/day. (Boe et al., 1989)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 9400 μg/cm^2 (RIFM, 2018)
Photoirritation/Photoallergenicity: Not expected to be a photoirritant/photoallergen. (UV/Vis Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC is available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence:
Screening-level: 2.54 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 551 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 1.874 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: 1.874 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.001874 μg/L

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

1. Identification

1. **Chemical Name:** Isoeugenyl benzyl ether
2. **CAS Registry Number:** 120-11-6
3. **Synonyms:** Benzene, 2-methoxy-1-(phenylmethoxy)-4-(1-propenyl)-; Benzyl isoeugenol; Benzyl 2-methoxy-4-propenylphenyl ether; 1-Benzyloxy-2-methoxy-4-propenylbenzene; iso-Eugenyl benzyl ether; 2-Methoxy-4-propenylphenyl benzyl ether; 4-Propenyl-1-(benzyloxy)-2-methoxybenzene; 2-ﾒﾄｷｼ-1-ﾌｴﾆﾙﾒﾄｷｼ-4-(1-ﾌﾟﾛﾍﾟﾆﾙﾍﾞﾝｾﾞﾝ); 1-(Benzyloxy)-2-methoxy-4-prop-1-en-1-ylbenzene; Isoeugenyl benzyl ether
4. **Molecular Formula:** $C_{17}H_{18}O_2$
5. **Molecular Weight:** 254.32 g/mol
6. **RIFM Number:** 285
7. **Stereochemistry:** No isomer specified. One geometric center and 2 total isomers are possible.

2. Physical data

1. **Boiling Point:** 356.34 °C (EPI Suite v4.11)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; closed cup (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 4.66 (EPI Suite v4.11)
4. **Melting Point**: 57 °C (FMA), 109.93 °C (EPI Suite v4.11)
5. **Water Solubility:** 2.344 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00000664 mm Hg at 20 °C (EPI Suite v4.0), 1.37e-005 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.065% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000081 mg/kg/day or 0.0054 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00097 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; B. Safford et al., 2015; B. Safford et al., 2024; B. 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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

1. Dermal: 40% SAM

Name	Isoeugenyl benzyl ether
J_{max} (μg/cm^2/h)	0.18*
Skin Absorption Class	40%

*J_{max} was calculated based on calculated log K_{ow} = 4.66 (EPI Suite

v4.11) and water solubility = 2.344 mg/L at 25 °C (EPI Suite v4.11).

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

6. Computational toxicology evaluation

1. **Cramer Classification**: Class III, High

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5 (OECD, 2021)
III	III	III

GRAS and EU-Flavis data.

9. REACH dossier

Available (ECHA, 2019); accessed on 05/17/23.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for isoeugenyl benzyl 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)	0.0017
2	Products applied to the axillae	0.22
3	Products applied to the face/body using fingertips	2.0
4	Products related to fine fragrances	4.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.0
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	1.0
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	1.0
5D	Baby cream, oil, talc	0.33
6	Products with oral and lip exposure	0.0017
7	Products applied to the hair with some hand contact	2.3
8	Products with significant ano-genital exposure (tampon)	0.33
9	Products with body and hand exposure, primarily rinse-off (bar soap)	7.8
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.7
10B	Aerosol air freshener	1.2
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.33
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 isoeugenyl benzyl ether, the basis was the subchronic reference dose of 0.80 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 9400 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; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.3.2.

2. Analogs Selected:

a. **Genotoxicity:** Isoeugenyl methyl ether (CAS # 93-16-3); Weight of Evidence (WoE) material: benzyl alcohol (CAS # 100-51-6)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Isoeugenyl methyl ether (CAS # 93-16-3)
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

Isoeugenyl benzyl 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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of isoeugenyl benzyl ether has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with isoeugenyl benzyl ether (solvent not specified) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2019). Under the conditions of the study, isoeugenyl benzyl ether was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of isoeugenyl benzyl ether; however, read-across can be made to isoeugenyl methyl ether (CAS # 93-16-3; see Section VI).

The clastogenic activity of isoeugenyl methyl ether was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with isoeugenyl methyl ether in dimethyl sulfoxide (DMSO) at concentrations up to 1780 μg/mL in the dose range

finding (DRF) study. In the main study, micronuclei analysis was conducted at concentrations up to 540 μg/mL in the presence and absence of metabolic activation. Isoeugenyl methyl ether did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, isoeugenyl methyl ether was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to isoeugenyl benzyl ether.

As additional WoE, the clastogenic activity of benzyl alcohol (CAS # 100-51-6) was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474 (Hayashi et al., 1988). Under the conditions of the study, benzyl alcohol was considered not to be clastogenic in the *in vivo* micronucleus test, and this can be extended to isoeugenyl benzyl ether.

Based on the data available, isoeugenyl methyl ether does not present a concern for genotoxic potential, and this can be extended to isoeugenyl benzyl ether.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/05/23.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. The repeated dose toxicity data on isoeugenyl benzyl ether are sufficient for the repeated dose toxicity endpoint. A gavage 28-day subchronic toxicity study was conducted in Wistar rats. Groups of 20 rats/sex/dose were administered 0, 60, 120, or 240 mg/kg/day of isoeugenyl benzyl ether diluted with soybean oil by gavage for 28 days. At 240 mg/kg/day, a reduction in food consumption was observed in both males and females, which caused the final body weights to be significantly decreased. A significant decrease in blood glucose and blood urea, with a significant increase in liver weights (relative and absolute), was also observed in the treated males and females. However, no histopathological changes were observed. At 120 mg/kg/day, a dose-related, non-significant reduction in feed consumption was observed in the females, which caused the final body weights to be significantly decreased. A significant decrease in the blood urea levels in females and the blood glucose levels in males and females was observed. No effects were reported at 60 mg/kg/day. Overall effects observed at the mid and high doses were not considered adverse. Thus,

Table 1
Summary of existing data on isoeugenyl methyl ether as a read-across for isoeugenyl benzyl ether.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm²	NOEL-HMT (induction) μg/cm²	LOEL[2] (induction) μg/cm²	WoE NESIL[3] μg/cm²	LLNA Weighted Mean EC3 Value μg/cm²	GPMT[4]	Buehler
Weak	9448	N/A	N/A	9400	N/A	Inconclusive	N/A
	In vitro Data				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	N/A	N/A	N/A		No alert found	No alert found	Schiff base formation; Michael addition

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; GPMT = Guinea Pig Maximization Test; LOEL = lowest observed effect level; 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]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Studies conducted according to the OECD TG 406 are included in the table.

the NOAEL was determined to be 240 mg/kg/day, based on decreased body weights and blood urea and glucose (Boe et al., 1989).

A default safety factor of 3 was used when deriving a NOAEL from 28-day studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity endpoint is 240/3 or 80 mg/kg/day.

Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 80/0.00097, or 82474.

In addition, the total systemic exposure to isoeugenyl benzyl ether (0.97 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.

11.1.2.2. Derivation of subchronic reference dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 0.80 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for isoeugenyl benzyl ether was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 80 mg/kg/day by the uncertainty factor, 100 = 0.80 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/20/23.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on isoeugenyl benzyl ether or any read-across materials. The total systemic exposure to isoeugenyl benzyl ether is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on isoeugenyl benzyl ether or any read-across materials that can be used to support the reproductive toxicity endpoint. The current total systemic exposure (0.97 μg/kg/day) is below the TTC for isoeugenyl benzyl ether (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/20/23.

11.1.4. Skin sensitization

Based on the existing data on the read-across material isoeugenyl methyl ether, isoeugenyl benzyl ether is a skin sensitizer with a defined NESIL of 9400 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 isoeugenyl benzyl ether. Therefore, isoeugenyl methyl ether (CAS # 93-16-3; see Section VI) was used for the risk assessment of isoeugenyl benzyl ether. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, isoeugenyl benzyl ether is a skin sensitizer. Isoeugenyl benzyl ether is predicted *in silico* to be reactive with skin proteins directly (however this alert is superseded by expert judgment based on experimental data demonstrating the aryl ring to be non-reactive), while read-across material isoeugenyl methyl ether is predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Therefore, this alert can be superseded due to expert judgment. Isoeugenyl benzyl ether was found to be inconclusive in a direct peptide reactivity assay (DPRA) (ECHA, 2019) and a human cell line activation test (h-CLAT) (ECHA, 2019) and positive in a KeratinoSens (ECHA, 2019). In a guinea pig maximization test, read-across material isoeugenyl methyl ether led to questionable skin sensitization reactions (RIFM, 1982). In a human maximization test, no skin sensitization reactions were observed when isoeugenyl benzyl ether was tested at 3450 μg/cm^2 (RIFM, 1972). In a human maximization test, no skin sensitization reactions were observed when read-across material isoeugenyl methyl ether was tested at 5520 μg/cm^2 (RIFM, 1972). In a Confirmation of No Induction in Humans (CNIH) test with 29525 μg/cm^2 of read-across material isoeugenyl methyl ether in 1:3 ethanol: diethyl phthalate (EtOH:DEP), reactions indicative of sensitization were observed in 1 of the 28 volunteers (RIFM, 2003a). In 4 separate CNIHs, read-across material isoeugenyl methyl ether did not present reactions indicative of sensitization. These negative CNIHs were conducted with 28 subjects at 29525 μg/cm^2 in 3:1 EtOH:DEP (RIFM, 2003b), 54 subjects at 23620 μg/cm^2 in 1:3 EtOH:DEP (RIFM, 2005), 27 subjects at 9448 μg/cm^2 in 3:1 EtOH:DEP (RIFM, 2004), and 24 volunteers at 9448 μg/cm^2 in 1:3 EtOH:DEP (RIFM, 2004). Additionally, in a CNIH test with 9448 μg/cm2 of read-across material isoeugenyl methyl ether in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 106 volunteers (RIFM, 2018).

Based on the WoE from structural analysis and *in vitro*, animal, and human studies on the read-across material and the target material, isoeugenyl benzyl ether is a sensitizer with a WoE NESIL of 9400 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 a subchronic RfD of 0.80 mg/kg/day.

Additional References: Natsch and Haupt, 2013; Itoh, 1982; Ishihara et al., 1986; Klecak, 1985.

Literature Search and Risk Assessment Completed On: 05/01/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, isoeugenyl benzyl ether would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation or photoallergy studies available for isoeugenyl benzyl ether in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. Based on the lack of absorbance, isoeugenyl benzyl ether does not present a concern for photoirritation or photoallergenicity.

11.1.6. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. As such, it is not a concern for photoirritant or photoallergenic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/24/23.

11.1.7. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for isoeugenyl benzyl ether is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.8. Risk assessment

There are no inhalation data available on isoeugenyl benzyl ether. Based on the Creme RIFM Model, the inhalation exposure is 0.0054 mg/day. This exposure is 87 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.874			1000000	0.001874	

Literature Search and Risk Assessment Completed On: 05/01/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of isoeugenyl benzyl 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 of 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 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, isoeugenyl benzyl 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 isoeugenyl benzyl ether 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 (2019), isoeugenyl benzyl 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.

11.2.1.2.3. Other available data. Isoeugenyl benzyl ether has been pre-registered for REACH with no additional data at this time.

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.

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

Exposure	Europe	North America
Log K_{ow} Used	4.6	4.6
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 0.001874 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 04/21/23.

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 01/23/24.

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.2024.114514.

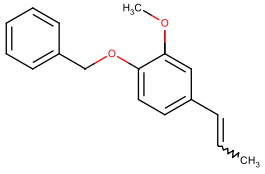
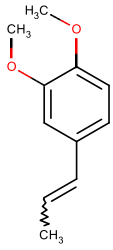
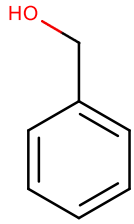
Appendix

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, 2021).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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	WoE Material
Principal Name	Isoeugenyl benzyl ether	Isoeugenyl methyl ether	Benzyl alcohol
CAS No.	120-11-6	93-16-3	100-51-6
Structure			
Similarity (Tanimoto Score)		0.71	0.25
SMILES	COc1cc(C=CC)ccc1OCc1ccccc1	COc1ccc(C=CC)cc1OC	OCc1ccccc1
Endpoint		Genotoxicity Skin sensitization	Genotoxicity
Molecular Formula	$C_{17}H_{18}O_2$	$C_{11}H_{14}O_2$	C_7H_8O
Molecular Weight (g/mol)	254.329	178.231	108.14
Melting Point (°C, EPI Suite)	109.93	18.00	−15.50
Boiling Point (°C, EPI Suite)	356.34	270.50	205.30
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.83E-03	1.20E+00	1.25E+01

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	WoE Material
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.34E+00	1.69E+02	4.29E+04
Log K_{OW}	4.66	2.95	1.1
J_{max} (μg/cm^2/h, SAM)	0.18	7.78	643.34
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.24E-01	1.54E+00	3.41E-02
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.5)	Michael addition|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450-mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	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 ≫ Arenes
Carcinogenicity (ISS)	No alert found	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	H-acceptor-path3-H-acceptor	H-acceptor-path3-H-acceptor	No alert found
Oncologic Classification	Not classified	Not classified	Not classified
Skin Sensitization			
Protein Binding (OASIS v1.1)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ benzyl phenyl ethers	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)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ benzyl phenyl ethers	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 v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on isoeugenyl benzyl ether (CAS # 120-11-6). 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, isoeugenyl methyl ether (CAS # 93-16-3) was identified as a read-across analog, and benzyl alcohol (CAS # 100-51-6) was identified as a WoE analog with sufficient data for toxicological evaluation.

Conclusions

- Isoeugenyl methyl ether (CAS # 93-16-3) was used as a read-across analog for the target material, isoeugenyl benzyl ether (CAS # 120-11-6), for the genotoxicity and skin sensitization endpoints.

  - The target material and the read-across analog are structurally similar and belong to the isoeugenyl group.
  - The key difference between the target material and the read-across analog is the target material has a benzyl group while the read-across analog has a methyl group. All major functionality is covered by the read-across material since the benzyl group is predicted to be stable. The major difference between the target material and the read-across analog is permeability, and since the read-across analog would have greater permeability, it would have greater bioavailability. 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.
  - 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.

- o Both the target material and the read-across analog have Michael addition alerts for DNA binding for genotoxicity. The data on the read-across analog confirms that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts and predictions are superseded by the data.
- o The target material and the read-across analog have Michael acceptor alerts for Skin Sensitization Reactivity Domains. The target material also has an alert for SN2 reactions at sp3 carbons for protein binding for skin sensitization due to the benzene group. The data on the read-across analog confirms that the material is a weak skin sensitizer. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts and predictions are consistent with the data.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Benzyl alcohol (CAS # 100-51-6) was used as a WoE analog for the target material, isoeugenyl benzyl ether (CAS # 120-11-6), for the genotoxicity endpoint.

- o The structural differences between the target material and the WoE analog are mitigated by the fact that the WoE analog could be a metabolite of the target material.
- o The similarity between the target material and the WoE analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- o The physical–chemical properties of the target material and the WoE analog are sufficiently similar to enable a comparison of their toxicological properties.
- o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the WoE analog.
- o Both the target material and the WoE analog have Michael addition alerts for DNA binding for genotoxicity. The data on the WoE analog confirms that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the WoE analog and the data on the WoE analog, the *in silico* alerts and predictions are superseded by the data.
- o The target material and the WoE analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the WoE analog and the target material.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Api, A.M., Basketter, D., Bridges, J., Cadby, P., et al., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 118, 104805.

Boe, M., Wurtzen, G., Olsen, P., 1989. Short term toxicity study in rats dosed with isoeugenol benzyl ether. Drug Chem. Toxicol. 12 (2), 165–171.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718.

ECHA, 2012. Guidance on information requirements and chemical safety assessment: chapter R.8: characterisation of dose [concentration]-response for human health. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017a. Guidance on information requirements and chemical safety assessment: chapter R.11: PBT Assessment. Retrieved from https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment. .

ECHA, 2017b. Read-across assessment framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

ECHA, 2019. Benzyl 2-methoxy-4-prop-1-enylphenyl ether registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/28352/1/2.

Hayashi, M., Kishi, M., Sofuni, T., Ishidate Jr., M., 1988. Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. Food Chem. Toxicol. 26 (6), 487–500.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2019. Volume of Use Survey, January-December 2019.

Ishihara, M., Itoh, M., Nishimura, M., Kinoshita, M., Kantoh, H., Nogami, T., Yamada, K., 1986. Closed epicutaneous test. Skin Res. 28 (Suppl. 2), 230–240.

Itoh, M., 1982. Sensitization potency of some phenolic compounds - with special emphasis on the relationship between chemical structure and allergenicity. J. Dermatol. (Tokyo) 9 (3), 223–233.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. In: Current Problems in Dermatology, 14, pp. 152–171.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352.

Natsch, A., Haupt, T., 2013. Utility of rat liver S9 fractions to study skin-sensitizing prohaptens in a modified keratinoSens assay. Toxicol. Sci. 135 (2), 356–368.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. https://one.oecd.org/document/ENV/JM/HA(2015)7/en/pdf.

OECD, 2021. The OECD QSAR Toolbox, v3.2–4.5. Retrieved from http://www.qsartoolbox.org/. .

RIFM (Research Institute for Fragrance Materials, Inc.), 1972. The Contact-Sensitization Potential of Fragrance Materials by Maximization Testing in Humans. Report to RIFM. RIFM Report Number 1804. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Guinea Pig Skin Sensitisation Test with Isoeugenyl Methyl Ether. Unpublished Report from Quest International. RIFM Report Number 46939. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2003a. Repeated Insult Patch Test (RIPT) with Isoeugenyl Methyl Ether. RIFM Report Number 44239. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2003b. Repeated Insult Patch Test (RIPT) with Isoeugenyl Methyl Ether. RIFM Report Number 44240. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated Insult Patch Test (RIPT) with Isoeugenyl Methyl Ether. RIFM Report Number 44241. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Repeated Insult Patch Test with Isoeugenyl Methyl Ether. RIFM Report Number 47345. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015. Isoeugenyl Methyl Ether: Micronucleus Test in Human Lymphocytes in Vitro. RIFM Report Number 68459. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Isoeugenyl Methyl Ether: Repeated Insult Patch Test (RIPT). RIFM Report Number 74381. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2019. Exposure Survey 25, October 2019.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2024. Corrigendum to "Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products". Regul. Toxicol. Pharmacol. 72 (3), 673-68]. Regul Toxicol Pharmacol. 105545.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.