Food and Chemical Toxicology 161 (2022) 112873

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, isoeugenyl ethyl ether, CAS Registry Number 7784-67-0

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[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, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[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 Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *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*
[k] *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*
[l] *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*
[m] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsum, 431-3192, Japan*

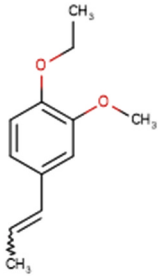
ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

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

https://doi.org/10.1016/j.fct.2022.112873
Received 7 October 2021; Received in revised form 15 December 2021; Accepted 14 February 2022
Available online 17 February 2022

Version: 100521. 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 ethyl ether CAS Registry Number: 7784-67-0

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (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

(*continued on next column*)

(*continued*)

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.

Isoeugenyl ethyl ether was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog isoeugenyl methyl ether (CAS # 93-16-3) show that isoeugenyl ethyl ether is not expected to be genotoxic and provided a NESIL of 9400 μg/cm^2 for the skin sensitization endpoint. Data on analogs isoeugenyl methyl ether (CAS # 93-16-3) and *trans*-methyl isoeugenol (CAS # 6379-72-2) provide a calculated MOE >100 for the repeated dose toxicity and reproductive toxicity endpoints, respectively. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; isoeugenyl ethyl ether is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material; exposure is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; for the hazard assessment based on the screening data, isoeugenyl ethyl ether is not PBT as per the IFRA Environmental Standards. For the risk assessment, isoeugenyl ethyl ether was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2014; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 33 mg/kg/day.	(Purchase et al., 1992)
Reproductive Toxicity: NOAEL = 272 mg/kg/day.	(ECHA REACH Dossier: 4-trans-Propenylveratrole; ECHA, 2017a)
Skin Sensitization: NESIL = 9400 μg/cm^2.	RIFM (2018)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Screening-level: 2.65 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 86.9 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Not applicable	

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: Not applicable; no Volume of Use reported for Europe and North America for 2015

1. Identification

1. **Chemical Name:** Isoeugenyl ethyl ether
2. **CAS Registry Number:** 7784-67-0
3. **Synonyms:** Benzene, 1-ethoxy-2-methoxy-4-(1-propenyl)-; 1-Ethoxy-2-methoxy-4-(1-propen-1-yl)benzene; 2-Ethoxy-5-propenylanisole; Ethyl isoeugenol; 1-Ethoxy-2-methoxy-4-prop-1-en-1-ylbenzene; Isoeugenyl ethyl ether
4. **Molecular Formula:** $C_{12}H_{16}O_2$
5. **Molecular Weight:** 192.25 g/mol
6. **RIFM Number:** 6860
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 271.2 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA)

3. **Log K_{OW}:** 3.44 (EPI Suite)
4. **Melting Point**: 43.69 °C (EPI Suite)
5. **Water Solubility:** 54.88 mg/L (EPI Suite)
6. **Specific Gravity**: Not Available
7. **Vapor Pressure:** 0.00335 mm Hg at 20 °C (EPI Suite v4.0), 0.006 mm Hg at 25 °C (EPI Suite)
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:** Arctander (1969): White crystals which have a mild, sweet, balsamic-Carnation-like, warm, and floral odor with a faintly spicy, vanilla-like undertone

3. Volume of use (Worldwide band)

1. <0.1 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Lipstick**: 0.004% (RIFM, 2019)

(No reported use in Fine Fragrance).

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00032 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; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
III	III	III

2. Analogs Selected:
   a. **Genotoxicity:** Isoeugenyl methyl ether (CAS # 93-16-3)
   b. **Repeated Dose Toxicity:** Isoeugenyl methyl ether (CAS # 93-16-3)
   c. **Reproductive Toxicity:** *trans*-Methyl isoeugenol (CAS # 6379-72-2)
   d. **Skin Sensitization:** Isoeugenyl methyl ether (CAS # 93-16-3)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

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

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

9. REACH dossier

Isoeugenyl ethyl ether has been pre-registered for 2010; no dossier available as of 10/05/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for isoeugenyl ethyl ether are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.72
2	Products applied to the axillae	0.22
3	Products applied to the face/body using fingertips	0.56
4	Products related to fine fragrances	0.56
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.56
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	0.56
5D	Baby cream, oil, talc	0.19
6	Products with oral and lip exposure	0.56
7	Products applied to the hair with some hand contact	0.56
8	Products with significant ano-genital exposure (tampon)	0.19
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.56
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.56
10B	Aerosol air freshener	0.56
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.19
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	0.56

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 ethyl ether, the basis was the reference dose of 0.33 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-I

FRA-Standards.pdf).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Isoeugenyl ethyl ether was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic and clastogenic activity of isoeugenyl ethyl ether; however, read-across can be made to isoeugenyl methyl ether (CAS # 93-16-3; see Section VI). The mutagenic activity of isoeugenyl methyl ether has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with isoeugenyl methyl ether in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2014). Under the conditions of the study, isoeugenyl methyl ether was not mutagenic in the Ames test, and this can be extended to isoeugenyl ethyl ether.

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 DMSO at concentrations up to 1780 μg/mL in the dose range finding (DRF) study. Micronuclei analysis was conducted at 540 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Isoeugenyl methyl ether did not induce binucleated cells with micronuclei when tested up to cytotoxic levels 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 ethyl ether.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are insufficient data for repeated dose toxicity endpoint on the target material isoeugenyl ethyl ether. Read-across material isoeugenyl methyl ether (CAS 93-16-3, see Section VI) has sufficient repeated dose toxicity data. In a GLP-compliant 28-day repeated dose toxicity study, Sprague Dawley rats (16/sex/dose) were fed a diet containing isoeugenyl methyl ether (98.5% purity with 11.8% of *cis*-isomer and 86.8% of *trans*-isomer) at concentrations equivalent to 0, 30, 100, and 300 mg/kg/day (dietary concentrations were based on target concentrations 30/27, 89/91, and 275/264 mg/kg/day for males/females, respectively) daily for 28–31 consecutive days. No recovery group was included in the study. Overall, no treatment-related adverse effects were observed in clinical signs, body weight, or feed consumption at any dose level. However, there were statistically significant changes in liver, kidney, and blood. The hematological evaluation revealed no differences between the treated groups and the control animals except increased lymphocytes and WBC counts at 300 mg/kg/day dose. Since these were isolated events, the effects were not considered to be treatment-related adverse events. The increased refractive index of urine in males and decreased volume of urine in females at 300 mg/kg/day were observed in the concentration test but not in the dilution test. Moreover, increased ketone bodies at 300 mg/kg/day in males did not reflect any serum glucose changes in the same dose group. In addition, the increase in the urine refractive index was not considered dose-related in either sex because the control values were unusually low, thus representing a treatment-related artifact. Statistically significant decreases in serum alkaline phosphatase and alanine aminotransferase activity were observed in females receiving the 300 mg/kg/day dose combined with an increase in liver weights in both male and female animals at 300 mg/kg/day. At 300 mg/kg/day, alanine aminotransferase activity was significantly elevated, and a significant increase in relative liver weight (10%–15%) was also observed in both sexes without correlating histopathological hepatic alterations with the exception of 1 female rat that underwent extensive liver necrosis. The European Chemicals Agency (ECHA) reported that the increase in ALT activity at 300 mg/kg/day was only 30% when compared with respective control animals. Since the change in ALT activity of less than a 2-fold magnitude is considered to be reversible (Hall et al., 2012), and the appearance of extensive necrosis was observed only in 1 animal, the increased liver weight was not considered to be a toxic response related to the treatment. Moreover, there were higher incidences of inflammatory lesions seen in the kidneys of the 300 mg/kg/day treated animals, which were not considered adverse since kidney lesions are frequently found in rats of the age range used in the study and were seen only in a few animals. Further, lesions in the Harderian gland were considered spontaneous, and in all cases, acinar degradation of the Harderian gland was minimal or mild and focal in its distribution. Such inflammatory and degenerative changes in the rat Harderian gland are commonly associated with sialodachryoadenitis (Otto, 2006). Therefore, its occurrence in the present study was not considered to be a direct effect of treatment. There were no further treatment-related histopathological alterations attributed to isoeugenyl methyl ether administration. Therefore, the NOAEL for systemic toxicity was considered to be 100 mg/kg/day (89 mg/kg/day and 91 mg/kg/day for male and female, respectively), based on no treatment-related effects observed (Purchase et al., 1992; RIFM, 1988; WHO, 2004; ECHA, 2017a). The most conservative NOAEL of 100 mg/kg/day for females was chosen for the risk assessment.

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

Thus, the derived NOAEL for the repeated dose toxicity data is 100/3 or 33 mg/kg/day.

Therefore, the isoeugenyl ethyl ether MOE for the repeated dose toxicity endpoint can be calculated by dividing the isoeugenyl methyl ether NOAEL in mg/kg/day by the total systemic exposure to isoeugenyl ethyl ether, 33/0.00032 or 103125.

In addition, the total systemic exposure to isoeugenyl ethyl ether (0.32 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.

11.1.2.1.1. 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. (RIFM, 2020) and a subchronic RfD of 0.33 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 ethyl ether was calculated by dividing the NOAEL of 33 mg/kg/day by the uncertainty factor, 100 = 0.33 mg/kg/day.

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

Additional References: RIFM, 1981; NTP, 2010; EMA, 2011; WHO, 2004.

Literature Search and Risk Assessment Completed On: 05/20/21.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on isoeugenyl ethyl ether. Read-across material *trans*-methyl isoeugenol (CAS # 6379-72-2; see Section VI) has sufficient developmental and reproductive toxicity data. In a GLP and OECD 421 compliant reproduction/developmental toxicity screening test, Crl:CD(SD) rats (10/sex/dose) were fed diets containing *trans*-methyl isoeugenol (4-*trans*-propenylveratrole) at concentrations of 0, 1500, 4500, or 15000 ppm (equivalent to average achieved doses of 0, 94, 272, or 769 mg/kg/day for males and 0, 103/113/207, 289/329/601, or 826/1008/1793 mg/kg/day for females, before mating, during gestation, and during lactation, respectively). Males were treated for 28 days, including 2 weeks prior to pairing and during the mating period, while females were treated starting 2 weeks prior to mating (including mating and gestation) until day 7 of lactation. At 15000 ppm, body weight was significantly reduced during the first week of treatment in both sexes, and bodyweight gain was reduced significantly for females receiving 15000 ppm from day 10 of gestation through lactation. Feed consumption was significantly reduced during week 1 of treatment at 15000 ppm in both sexes, and at 4500 and 15000 ppm throughout the study for females (feed intake of males was normal from week 2). Furthermore, no treatment-related effects on pre-coital interval, mating performance, fertility, and gestation length/index were observed. The number of implantations, post-implantation survival index, and litter size were significantly reduced in females receiving the 15000 ppm dose. However, there were no treatment-related effects on the live birth index, viability index, and sex ratio. Clinical observations of offspring showed an increased incidence of pups being cold to the touch and/or little milk in the stomach at 15000 ppm. Furthermore, there was a significant reduction in offspring body weights between post-natal day 1 and day 7. Macroscopic examination of pups euthanized before lactation day 7 revealed an increased incidence of no milk in the stomach for offspring at 15000 ppm and a thin build was apparent among offspring in 2 litters at age day 7. The causes for the cold to touch and/or little milk in the stomach, and reduced growth in the offspring could not be determined. However, in the absence of significant effects during macroscopic examination and histopathology, it was considered that these effects were mediated through the reduced feed consumption of the dam during lactation and/or unpalatability of the *trans*-methyl isoeugenol secreted in the milk. Therefore, the NOAEL for systemic toxicity in dams was considered to be 4500 ppm (equivalent to daily intakes between 289 and 601 mg/kg/day depending on the sex, age, and weight of the animals), based on a significant reduction in bodyweight gain among higher dose females. The NOAEL for reproduction and developmental toxicity was considered to be 4500 ppm (equivalent to daily intakes between 272 and 601 mg/kg/day depending on the sex, age, and weight of the animals), based on the effects on implantations, post-implantation survival index, litter size, and fetal growth at 15000 ppm (ECHA, 2017a). A NOAEL of 272 mg/kg/day was selected for the reproductive toxicity endpoint.

Therefore, the isoeugenyl ethyl ether MOE for the reproductive toxicity endpoint can be calculated by dividing *trans*-methyl isoeugenol NOAEL in mg/kg/day by the total systemic exposure to isoeugenyl ethyl ether, 272/0.00032 or 850000.

In addition, the total systemic exposure to isoeugenyl ethyl ether (0.32 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/31/21.

11.1.4. Skin sensitization

Based on the existing data for read-across isoeugenyl methyl ether (CAS # 93-16-3), isoeugenyl ethyl ether is considered to be a skin sensitizer with a defined NESIL of 9400 μg/cm^2.

11.1.4.1. Risk assessment. No skin sensitization studies are available for isoeugenyl ethyl ether. Based on the existing data and read-across material isoeugenyl methyl ether (CAS # 93-16-3; see Section VI), isoeugenyl ethyl ether is considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0). No *in vitro* or *in chemico* studies were available for the target material and the read-across material. In a guinea pig maximization test with the read-across material isoeugenyl methyl ether reactions indicative of sensitization were seen at 5% (RIFM, 1982). However, in 2 closed and 2 open epicutaneous tests performed in guinea pigs with the read-across material, reactions indicative of sensitization were not observed (Itoh, 1982; Ishihara et al., 1986; Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with the read-across material isoeugenyl methyl ether at 8% (RIFM, 1972). In a Confirmation of No Induction in Humans test (CNIH) with the read-across material isoeugenyl methyl ether tested at 25% (29,527 μg/cm2) in 3:1 ethanol:diethyl phthalate (EtOH:DEP), reactions indicative of sensitization were observed in 1/28 volunteers (RIFM, 2003a). In other CNIHs, isoeugenyl methyl ether did not present reactions indicative of sensitization when tested at 25% (29,527 μg/cm^2) in 3:1 EtOH:DEP in 28 volunteers (RIFM, 2003b), at 20% (23,622 μg/cm2) in 3:1 EtOH:DEP in 54 volunteers (RIFM, 2005), or at 8% (9448 μg/cm2) in 27 and 24 volunteers (RIFM, 2004). Another CNIH with 106 volunteer subjects did not present any reactions indicative of skin sensitization when 8% (9448 μg/cm^2) of the read-across material isoeugenyl methyl ether in 1:3 EtOH:DEP was used for induction and challenge (RIFM, 2018).

Based on the available data on read-across material isoeugenyl methyl ether, summarized in Table 1, isoeugenyl ethyl ether is considered to be a skin sensitizer with a defined NESIL of 9400 μg/cm^2. Section X provides the maximum acceptable concentrations in finished

Table 1
Data summary for isoeugenyl methyl ether as read-across material for isoeugenyl ethyl ether.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[3] μg/cm^2
N/A	N/A	9448	5520	29,527	9400

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a subchronic RfD of 0.33 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/27/21.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for isoeugenyl ethyl ether in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, Isoeugenyl ethyl ether does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/21.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on isoeugenyl ethyl ether. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is 4700 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/28/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of isoeugenyl ethyl ether was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, Isoeugenyl ethyl ether was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified isoeugenyl ethyl 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, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Not applicable.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

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

11.2.3. Risk assessment refinement

Not applicable.

Literature Search and Risk Assessment Completed On: 05/24/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

  Search keywords: CAS number and/or material names

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 10/05/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112873.

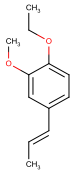
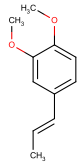
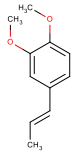
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical 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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Isoeugenyl ethyl ether	Isoeugenyl methyl ether	*trans*-Methyl isoeugenol
CAS No.	7784-67-0	93-16-3	6379-72-2
Structure			
Similarity (Tanimoto Score)		0.88	0.88
Read-across Endpoint		• Genotoxicity • Skin Sensitization • Repeated Dose Toxicity	• Reproductive Toxicity
Molecular Formula	$C_{12}H_{16}O_2$	$C_{11}H_{14}O_2$	$C_{11}H_{14}O_2$
Molecular Weight (g/mol)	192.25	178.23	178.23
Melting Point (°C, EPI Suite)	43.69	18	18
Boiling Point (°C, EPI Suite)	271.20	270.5	270.5
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.801	1.2	1.2
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.44	2.95	2.95
Water Solubility (μg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	54.88	169.1	169.1
J_{max} (μg/cm^2/h, SAM)	6.528	12.359	12.359

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.04E+000	1.54E+000	1.54E+000
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Hydroquinones	
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	
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	• Not classified	• Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized	• Curcumin (Renal toxicity) Alert • Methoxamine (Renal toxicity) Alert	
Reproductive and Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group		• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (moderate reliability)		• Non-toxicant (moderate reliability)
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found	• No alert found	
Protein Binding (OECD)	• No alert found	• No alert found	
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• Alert for Michael acceptor	• Alert for Michael acceptor	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3

Summary

There are insufficient toxicity data on isoeugenyl ethyl ether (CAS # 7784-67-0). 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) and *trans*-methyl isoeugenol (CAS # 6379-72-2) were identified as read-across analogs 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 ethyl ether (CAS # 7784-67-0) for the genotoxicity, repeated dose toxicity, and skin sensitization endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of isoeugenyl. Isomer in the read-across analog is not specified.
  - The target material and the read-across analog share an isoeugenyl group with an ether group.
  - The key difference between the target material and the read-across analog is that the target material has an ethoxy group, whereas the read-across analog has a methoxy group in the same position. This structural difference is toxicologically insignificant.
  - 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 comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target and read-across materials have an *In Vivo* Mutagenicity (Micronucleus, ISS) for H-acceptor-path3-H-acceptor. This alert is due to the ether oxygens within 1–4 connectivity. The data described in the genotoxicity section shows that the MOE is adequate at the current level of use. The predictions are superseded by the data.
  - Both the target material and the read-across analog have a Skin Sensitization Reactivity Domains by Toxtree v2.6.13 alert for Michael acceptor. This alert is due to the unsaturated branch in the isoeugenyl moiety. The data described in the skin sensitization section confirm that the target material is a skin sensitizer. Therefore, *in silico* alerts are consistent with the data.
  - The read-across analog has a DNA Binding (OECD) Michael addition alert for hydroquinones, which is due to the 1,2 methylether groups. Moreover, the read-across analog has 2 Repeated Dose (HESS) alerts for curcumin and methoxamine renal toxicity due to structural similarities of 55% with the former and 57.1% with the latter using the Dice score. According to these predictions, the read-across analog is expected to be

more reactive compared to the target material. Data superseded predictions in this case.
  - 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.
- *trans*-Methyl isoeugenol (CAS # 6379-72-2) was used as a read-across analog for the target material isoeugenyl ethyl ether (CAS # 7784-67-0) for the reproductive toxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of isoeugenyl.
  - The target material and the read-across analog share an isoeugenyl group with an ether group.
  - The key difference between the target material and the read-across analog is that the target material has an ethoxy group, while the read-across analog has a methoxy group in the same position. This structural difference is toxicologically insignificant.
  - 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 comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog 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.

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.

Arctander, S., 1969. Perfume and Flavor Chemicals (Aroma Chemicals), vols. I and II. Published by the author: Montclair, NJ (USA).

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.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2017a. 4-*trans*-Propenylveratrole Registration Dossier. Retrieved from. https://echa.europa.eu/en/registration-dossier/-/registered-dossier/18980.

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

EMA, 2011. European Public MRL Assessment Report (EPMAR) Isoeugenol (Fin Fish). Retrieved from. https://www.ema.europa.eu/documents/mrl-report/isoeugenol-fin-fish-european-public-mrl-assessment-report-epmar-committee-medicinal-products_en.pdf.

Hall, A.P., Elcombe, C.R., Foster, J.R., Harada, T., Kaufmann, W., et al., 2012. Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes–conclusions from the 3rd International ESTP expert workshop. Toxicol. Pathol. 40 (7), 971–994.

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), 2015. Volume of Use Survey, February 2015.

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. Curr. Probl. Dermatol. 14, 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, 2021 Sep-Oct 01.

National Toxicology Program, 2010. Toxicology and Carcinogenesis Studies of Isoeugenol (CAS No. 97-54-1) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP-TR-551, Unpublished.

OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

Otto, 2006. The Laboratory Rat (Chapter 16), second ed. Medical Management and Diagnostic Approaches. Retrieved from: https://doi.org/10.1016/B978-012074903-4/50019-4.

Purchase, R., Ford, G.P., Creasy, D.M., Brantom, P.G., Gangolli, S.D., 1992. A 28-day feeding study with methyl isoeugenol in rats. Food Chem. Toxicol. 30 (6), 475–481.

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, 1981. A 91-day Single Dose Level Dietary Study of Eugenyl Methyl Ether and Isoeugenyl Methyl Ether in the Albino Rat. Report to FEMA. Unpublished Report from Osborne, B.E., Plawiuk, M., Graham, C., Bier, C., Losos, G., Broxup, B. & Procter, B.C. RIFM Report Number 5698. 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, 1988. A 28-day Feeding Study with Isoeugenyl Methyl Ether in Rats. Private Communication from IOFI Unpublished Report from Purchase, R., Gangolli, S.D. & Brantom, P.G. RIFM Report Number 10538. 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, 2013. Report on the Testing of Isoeugenyl Ethyl Ether in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 66980. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2014. Isoeugenyl Methyl Ether: Reverse Mutation Assay "Ames Test" Using Salmonella typhimurium and Escherichia coli. RIFM Report Number 67268. 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 24, March 2019.

RIFM Research Institute for Fragrance Materials, Inc, 2020. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM Report Number 76775. RIFM, Woodcliff Lake, NJ, USA.

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., 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.
WHO, 2004. WHO Food Additive Series 52, Hydroxypropenylbenzenes (Addendum). Retrieved from. http://www.inchem.org/documents/jecfa/jecmono/v52je17.htm.