Food and Chemical Toxicology 189 (2024) 114552

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

# RIFM fragrance ingredient safety assessment, isoeugenyl phenylacetate, CAS registry number 120-24-1

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

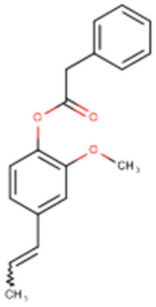
Handling Editor: Dr. Bryan Delaney

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

https://doi.org/10.1016/j.fct.2024.114552
Received 30 January 2024; Received in revised form 12 February 2024; Accepted 28 February 2024
Available online 7 March 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: http://fragrancematerialsafetyresource.elsevier.com.

**Name:** Isoeugenyl phenylacetate
**CAS Registry Number:** 120-24-1



**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**CAESAR -** Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
**CNIH** - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
**Creme RIFM Model** - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; 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

(*continued on next column*)

(*continued*)

**WoE** - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Isoeugenyl phenylacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog isoeugenol benzoate (CAS # 4194-00-7) show that isoeugenyl phenylacetate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to isoeugenyl phenylacetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog isoeugenyl acetate (CAS # 93-29-8) provided isoeugenyl phenylacetate a No Expected Sensitization Induction Level (NESIL) of 2300 μg/cm$^2$ for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; isoeugenyl phenylacetate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; isoeugenyl phenylacetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

**Human Health Safety Assessment**

**Genotoxicity:** Not expected to be genotoxic. (RIFM, 2017; RIFM, 2018)
**Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC.
**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.
**Skin Sensitization:** NESIL = 2300 μg/cm$^2$. (RIFM, 2000a; RIFM, 2000b)
**Photoirritation/Photoallergenicity:** Not expected to be photoirritating/photoallergenic (UV/Vis Spectra; RIFM Database
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:**
Screening-level: 2.06 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
**Bioaccumulation:**
Screening-level: 580 L/kg (EPI Suite v4.11; US EPA, 2012a)
**Ecotoxicity:**
Screening-level: Fish LC50: 2.081 mg/L (RIFM Framework; Salvito, 2002)
**Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards
**Risk Assessment:**
**Screening-level:** PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito, 2002)
**Critical Ecotoxicity Endpoint:** Fish LC50: 2.081 mg/L (RIFM Framework; Salvito, 2002)
**RIFM PNEC is:** 0.002081 μg/L
- **Revised PEC/PNECs (2019 IFRA VoU):** North America (not reported) and Europe: not applicable; cleared at the screening-level

## 1. Identification

1. **Chemical Name:** Isoeugenyl phenylacetate

2. **CAS Registry Number:** 120-24-1
3. **Synonyms:** Benzeneacetic acid, 2-methoxy-4-(1-propenyl)phenyl ester; Isoeugenyl α-toluate; 2-Methoxy-4-(1-propen-1-yl)phenyl phenylacetate; 2-Methoxy-4-propenylphenyl phenylacetate; 4-Propenylguaiacyl phenylacetate; 2-Methoxy-4-prop-1-en-1-ylphenyl phenylacetate; Isoeugenyl phenylacetate
4. **Molecular Formula:** $C_{18}H_{18}O_3$
5. **Molecular Weight:** 282.33 g/mol
6. **RIFM Number:** 1232
7. **Stereochemistry:** No isomer specified. One geometric center and 2 total isomers are possible.

## 2. Physical data

1. **Boiling Point:** 382.06 °C (EPI Suite v4.11)
2. **Flash Point:** >200 °F; closed cup (Fragrance Materials Association [FMA])
3. **Log $K_{OW}$:** 4.69 (EPI Suite v4.11)
4. **Melting Point**: 125.22 °C (EPI Suite v4.11)
5. **Water Solubility:** 1.526 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 1.115 (FMA), 1.117–1.121 (Givaudan Specification Sheet, 1983)
7. **Vapor Pressure:** 0.00000106 mm Hg at 20 °C (EPI Suite v4.0), 2.26e-006 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficients (36, 46, 274 L $mol^{-1}$ • $cm^{-1}$ under neutral, acidic, and basic conditions, respectively) are below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** A yellow viscous liquid with a mild sweet clove and honey odor.

## 3. Volume of use (Worldwide band)

| | |
|---|---|
| 1. <0.1 metric ton per year | IFRA (2019) |

## 4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.5)

| | |
|---|---|
| **95**th **Percentile Concentration in Fine Fragrance:** 0.0024% | RIFM (2021) |
| **2. Inhalation Exposure*:** 0.00000028 mg/kg/day or 0.00018 mg/day | RIFM (2021) |
| **3. Total Systemic Exposure**:** 0.000040 mg/kg/day | RIFM (2021) |

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

## 6. Computational toxicology evaluation

### 6.1. *Cramer Classification:* Class I, Low

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.5 |
|---|---|---|
| I | I | I |

### 6.2. *Analogs Selected*

a. **Genotoxicity:** Isoeugenol benzoate (CAS # 4194-00-7)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Isoeugenyl acetate (CAS # 93-29-8); Weight of Evidence (WoE) material: Ethyl phenylacetate (CAS # 101-97-3)
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 phenylacetate 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 phenylacetate has been pre-registered for 2010; no dossier is available as of 01/23/24.

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for isoeugenyl phenylacetate 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) | 0.18 |
| 2 | Products applied to the axillae | 0.053 |
| 3 | Products applied to the face/body using fingertips | 1.1 |
| 4 | Products related to fine fragrances | 0.99 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.25 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.25 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.25 |
| 5D | Baby cream, oil, talc | 0.25 |
| 6 | Products with oral and lip exposure | 0.58 |
| 7 | Products applied to the hair with some hand contact | 2.0 |

(*continued on next page*)

(*continued*)

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%)[c] |
|---|---|---|
| 8 | Products with significant ano-genital exposure (tampon) | 0.10 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 1.9 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 6.9 |
| 10B | Aerosol air freshener | 6.9 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 3.8 |
| 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 phenylacetate, the basis was a skin sensitization NESIL of 2300 μg/cm$^2$.

bFor 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).

cCalculations by Creme RIFM Aggregate Exposure Model v3.3.2.

## 11. Summary

### *11.1. Human health endpoint summaries*

#### *11.1.1. Genotoxicity*

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

*11.1.1.1. Risk assessment.* There are no studies assessing the mutagenic or clastogenic activity of isoeugenyl phenylacetate; however, read-across can be made to isoeugenol benzoate (CAS # 4194-00-7; see Section VI).

The mutagenic activity of isoeugenol benzoate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with isoeugenol benzoate in acetone 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, 2017). Under the conditions of the study, isoeugenol benzoate was not mutagenic in the Ames test, and this can be extended to isoeugenyl phenylacetate.

The clastogenic activity of isoeugenol benzoate 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 isoeugenol benzoate in acetone at concentrations up to 2000 μg/mL in the dose range finding (DRF) study. In the main study, micronuclei analysis was conducted at concentrations up to 200 μg/mL in the presence and absence of metabolic activation. Isoeugenol benzoate did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2018). Under the conditions of the study, isoeugenol benzoate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to isoeugenyl phenylacetate.

Based on the data available, isoeugenol benzoate does not present a concern for genotoxic potential, and this can be extended to isoeugenyl phenylacetate.

**Additional References:** None.

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

#### *11.1.2. Repeated dose toxicity*

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

*11.1.2.1. Risk assessment.* There are no repeated dose toxicity data on isoeugenyl phenylacetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to isoeugenyl phenylacetate (0.04 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**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 phenylacetate or any read-across materials. The total systemic exposure to isoeugenyl phenylacetate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

*11.1.3.1. Risk assessment.* There are no reproductive toxicity data on isoeugenyl phenylacetate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to isoeugenyl phenylacetate (0.04 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I 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 read-across material isoeugenyl acetate and WoE material ethyl phenylacetate, isoeugenyl phenylacetate was assigned a NESIL of 2300 μg/cm$^2$, and the maximum acceptable concentrations in finished products are provided in Section X.

*11.1.4.1. Risk assessment.* No skin sensitization data are available for isoeugenyl phenylacetate. Therefore, a structurally related material, isoeugenyl acetate (CAS # 93-29-8; see Section VI), was used for the risk assessment of isoeugenyl phenylacetate. The data on the read-across material are summarized in Table 1. Additionally, ethyl phenylacetate (CAS # 101-97-3; see Section VI) was used as WoE. Isoeugenyl phenylacetate, read-across material isoeugenyl acetate, and WoE material ethyl phenylacetate are predicted *in silico* to be non-reactive with skin proteins directly (Roberts, 2007; OECD Toolbox v4.5). WoE material ethyl phenylacetate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and human cell line activation test (h-CLAT) (RIFM, 2016b; RIFM, 2016a). The results were evaluated following the OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a), and based on the 2 out of 3 Defined Approach, WoE material ethyl phenylacetate is a non-sensitizer. In a murine local lymph node assay (LLNA), isoeugenyl acetate was not found to be non-sensitizing when tested up to 25% (6250 μg/cm2) (RIFM, 2005). In 2 separate guinea pig closed epicutaneous tests (CET), read-across material isoeugenyl acetate showed reactions indicative of sensitization (Itoh, 1982; Ishihara, 1986). However, in a guinea pig open epicutaneous test (OET), read-across material isoeugenyl acetate and WoE ethyl phenylacetate did not present reactions indicative of sensitization (Klecak, 1979, 1985). In 2 separate human maximization tests, no skin

**Table 1**
Summary of existing data on isoeugenyl acetate as a read-across for isoeugenyl phenylacetate.

| WoE Skin Sensitization Potency Category[1] | Human Data | | | | Animal Data | | |
|---|---|---|---|---|---|---|---|
| | NOEL-CNIH (induction) µg/cm² | NOEL-HMT (induction) µg/cm² | LOEL (induction) µg/cm² | WoE NESIL[2] µg/cm² | LLNA[3] Weighted Mean EC3 Value µg/cm² | GPMT | Buehler |
| Weak | 2362 | 10350 | N/A | 2300 | Negative up to 6250 (25%) | N/A | 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 |

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.
1WoE 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).
2WoE NESIL limited to 2 significant figures.
3Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).

sensitization reactions were observed when read-across material isoeugenyl acetate was tested at 10350 µg/cm2 and 6900 µg/cm2 (RIFM, 1974; RIFM, 1973b). In a human maximization test, no skin sensitization reactions were observed when WoE ethyl phenylacetate was tested at 5520 µg/cm2 (RIFM, 1973a). Additionally, in 2 Confirmation of No Induction in Humans tests (CNIHs) with 2362 µg/cm2 of read-across material isoeugenyl acetate in 3:1 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 54 and 49 volunteers, respectively (RIFM, 2000a; RIFM, 2000b).

Based on the WoE from structural analysis and *in vitro*, animal, and human studies on the read-across material isoeugenyl acetate, WoE material ethyl phenylacetate, and the target material, isoeugenyl phenylacetate was assigned a WoE NESIL of 2300 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).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 05/03/23.

*11.1.5. Photoirritation/photoallergenicity*

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

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

*11.1.5.2. UV spectra analysis.* UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficients (36, 46, 274 L mol$^{-1}$ • cm$^{-1}$ under neutral, acidic, and basic conditions, respectively) are below the benchmark of concern for photoirritating effects, 1000 L mol$^{-1}$ • cm$^{-1}$ (Henry et al., 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 05/02/23.

*11.1.6. Local respiratory toxicity*

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for isoeugenyl phenylacetate is below the Cramer Class I TTC value for inhalation exposure local effects.

*11.1.6.1. Risk assessment.* There are no inhalation data available on isoeugenyl phenylacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.00018 mg/day. This exposure is 7777.8 times lower than the Cramer Class I TTC value of 1.4 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:** 05/01/23.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of isoeugenyl phenylacetate was performed following the RIFM Environmental Framework (Salvito, 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 phenylacetate 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 phenylacetate 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).

*11.2.2. Risk assessment*

Based on the current VoU (2019), isoeugenyl phenylacetate presents no risk to the aquatic compartment in the screening-level assessment.

*11.2.2.1. Key studies.* Biodegradation

No data available.

Ecotoxicity

No data available.

Other available data

Isoeugenyl phenylacetate has been pre-registered for REACH with no additional data.

*11.2.3. Risk assessment refinement*

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

Endpoints used to calculate PNEC are underlined.

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | <u>2.081</u> | | | 1000000 | 0.002081 | |

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito, 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 | Not reported |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

The RIFM PNEC is 0.002081 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

**Literature Search and Risk Assessment Completed On:** 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.2024.114552.

## Appendix

*Read-across Justification*

*Methods*

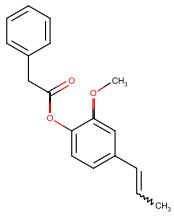
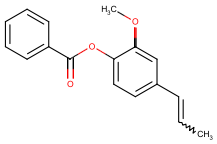
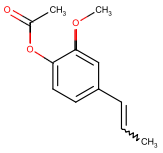
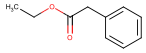
The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015)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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- $J_{max}$ values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021b).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

| | Target Material | Read-across Material | Read-across Material | WoE Material |
|---|---|---|---|---|
| **Principal Name** | isoeugenyl phenylacetate | Isoeugenol benzoate | Isoeugenyl acetate | Ethyl phenylacetate |
| **CAS No.** | 120-24-1 | 4194-00-7 | 93-29-8 | 101-97-3 |

(*continued on next page*)

(*continued*)

| | Target Material | Read-across Material | Read-across Material | WoE Material |
|---|---|---|---|---|
| **Structure** |  |  |  |  |
| **Similarity (Tanimoto Score)** | | 0.64 | 0.76 | 0.38 |
| **SMILES** | COc1cc(C=CC)ccc1OC(=O)Cc1ccccc1 | COc1cc(C=CC)ccc1OC(=O)c1ccccc1 | COc1cc(C=CC)ccc1OC(C)=O | CCOC(=O)Cc1ccccc1 |
| **Endpoint** | | Genotoxicity | Skin sensitization | Skin sensitization |
| **Molecular Formula** | $C_{18}H_{18}O_3$ | $C_{17}H_{16}O_3$ | $C_{12}H_{14}O_3$ | $C_{10}H_{12}O_2$ |
| **Molecular Weight (g/mol)** | 282.339 | 268.312 | 206.241 | 164.204 |
| **Melting Point (°C, EPI Suite)** | 125.22 | 116.95 | 59.35 | −29.40 |
| **Boiling Point (°C, EPI Suite)** | 382.06 | 370.46 | 290.44 | 227.00 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 3.01E-04 | 7.05E-04 | 2.07E-01 | 1.22E+01 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 1.53E+00 | 3.02E+00 | 1.15E+02 | 7.39E+02 |
| **Log $K_{OW}$** | 4.69 | 4.44 | 2.99 | 2.28 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 0.08 | 0.15 | 2.97 | 17.82 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 2.52E-02 | 6.18E-02 | 3.12E-01 | 1.90E+00 |
| ***Genotoxicity*** | | | | |
| **DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)** | 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 | No alert found | | |
| **Carcinogenicity (ISS)** | No alert found | No alert found | | |
| **DNA Binding (Ames, MN, CA, OASIS v1.1)** | No alert found | No alert found | | |
| ***In Vitro* Mutagenicity (Ames, ISS)** | No alert found | No alert found | | |
| ***In Vivo* Mutagenicity (Micronucleus, ISS)** | H-acceptor-path3-H-acceptor | H-acceptor-path3-H-acceptor | | |
| **Oncologic Classification** | Not classified | Not classified | | |
| ***Skin Sensitization*** | | | | |
| **Protein Binding (OASIS v1.1)** | No alert found | | No alert found | No alert found |
| **Protein Binding (OECD)** | Acylation\|Acylation ≫ Direct Acylation Involving a Leaving group\|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates | | Acylation\|Acylation ≫ Direct Acylation Involving a Leaving group\|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates | No alert found |
| **Protein Binding Potency** | Not possible to classify according to these rules (GSH) | | 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 | No alert found |
| **Skin Sensitization Reactivity Domains (Toxtree v2.6.13)** | Alert for Michael Acceptor identified | | Alert for Michael Acceptor identified | No skin sensitization reactivity domain alerts were identified |
| ***Metabolism*** | | | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)** | See Supplemental Data 1 | See Supplemental Data 2 | See Supplemental Data 3 | See Supplemental Data 4 |

*Summary*

There are insufficient toxicity data on isoeugenyl phenylacetate (CAS # 120-24-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, Isoeugenol benzoate

(CAS # 4194-00-7), isoeugenyl acetate (CAS # 93-29-8), and ethyl phenylacetate (CAS # 101-97-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

*Conclusions*

- Isoeugenol benzoate (CAS # 4194-00-7) was used as a read-across analog for the target material, isoeugenyl phenylacetate (CAS # 120-24-1), for the genotoxicity endpoint.
  - o The target material and the read-across analog share a commonality in that they are both aryl esters of isoeugenol.
  - o The key difference between the target material and the read-across analog is that the read-across analog is a benzyl ester, whereas the target material is a phenyl ester. 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.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o Differences are predicted for $J_{max}$, which estimates skin absorption. $J_{max}$ for the target material corresponds to skin absorption $\leq$10%, and $J_{max}$ for the read-across analog corresponds to skin absorption $\leq$40%. While the percentage of skin absorption estimated from $J_{max}$ indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o 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 read-across analog have alerts for H-acceptor-path3-H-acceptor, while the target material alone has an *in silico* alert for P450-mediated activation to Quinones and Quinone-type Chemicals. The data from the genotoxicity section confirms that the material is of non-concern for genotoxicity. Therefore, the predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Isoeugenyl acetate (CAS # 93-29-8) was used as a read-across analog along with ethyl phenylacetate (CAS # 101-97-3) as a WoE material for the target material, isoeugenyl phenylacetate (CAS # 120-24-1), for the skin sensitization endpoint.
  - o The target material and the read-across analog share a commonality in that they are both esters of isoeugenol.
  - o The key difference between the target material and the read-across analog is that the read-across analog is a methyl acetate, whereas the target material is a phenylacetate. Therefore, to satisfy the structural domain of the target material, the substance ethyl phenylacetate (CAS # 101-97-3) is used as WoE. This chemical has the same phenyl acetate structure as the target material. The read-across analog, combined with the WoE material, 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.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o Differences are predicted for $J_{max}$, which estimates skin absorption. $J_{max}$ for the target material corresponds to skin absorption $\leq$10%, and $J_{max}$ for the read-across analog corresponds to skin absorption $\leq$40%. While the percentage of skin absorption estimated from $J_{max}$ indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o 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 There are no *in silico* alerts for the WoE material, whereas both the read-across analog and the target material contain alerts for Michael acceptor and acylation. The data from the skin sensitization section confirms that the material is of non-concern for skin sensitization. Therefore, the predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

## 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.

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, 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.

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., 1979. The open epicutaneous test (OET), a predictive test procedure in the Guinea pig for estimation of allergenic properties of simple chemical compounds, their mixtures and of finished cosmetic preparations. Int. Federat. Soci. Cosmet. Chem. 9/18/79.
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.
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, 2021a. Guideline No. 497: Defined Approaches on Skin Sensitisation, OECD Guidelines for the Testing of Chemicals, Section 4. OECD Publishing, Paris. https://doi.org/10.1787/b92879a4-en retrieved from.
OECD, 2021b. The OECD QSAR Toolbox, v3.2–4.5. Retrieved from. http://www.qsartoolbox.org/.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973a. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1802.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973b. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1803.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1801.
RIFM (Research Institute for Fragrance Materials, Inc.), 2000a. Repeated Insult Patch Test (RIPT) of Isoeugenyl Acetate in Humans. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 35750.
RIFM (Research Institute for Fragrance Materials, Inc.), 2000b. Repeated Insult Patch Test (RIPT) of Isoeugenyl Acetate in Humans. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 35752.
RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Isoeugenyl Acetate: Local Lymph Node Assay. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 51633.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. Ethyl Phenylacetate: in Vitro Skin Sensitization Test - Human Cell Line Activation Test (H-CLAT). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 71266.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Ethyl Phenylacetate: Direct Peptide Reactivity Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 73339.
RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Isoeugenol Benzoate: Bacterial Reverse Mutation Assay. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 72930.
RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Isoeugenol Benzoate: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 74448.
RIFM (Research Institute for Fragrance Materials, Inc.), 2021. Exposure Surv. 32. August 2021.
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.