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Short Review

RIFM fragrance ingredient safety assessment, propenylguaethol, CAS Registry Number 94-86-0

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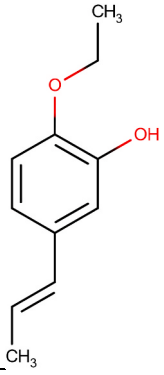
Version: 081020. This version replaces any previous versions.

Name: Propenylguaethol CAS Registry Number: 94-86-0



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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
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) 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

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(*continued*)

EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
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, 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.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(Heck, 1989; Wild, 1983)
Repeated Dose Toxicity: NOAEL = 37.5 mg/kg/day.	NTP (2010)
Developmental and Reproductive Toxicity: NOAEL = 500 and 230 mg/kg/day, respectively	(George, 2001; NTP, 2002)
Skin Sensitization: NESIL = 2300 μg/cm^2.	RIFM (1991)
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: 2.8 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 55.07 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 2.09 mg/L	(ECOSAR; US EPA, 2012b)
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: 48-h *Daphnia magna* LC50: 2.09 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.209 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** Propenylguaethol
2. **CAS Registry Number:** 94-86-0
3. **Synonyms:** 6-Ethoxy-*m*-anol; 1-Ethoxy-2-hydroxy-4-propenylbenzene; 2-Ethoxy-5-propenylphenol; Phenol, 2-ethoxy-5-(1-propenyl)-; 3-Propenyl-6-ethoxyphenol; Vanitrope; o-エトキシ-m-プロペニルフェノール; 2-Ethoxy-5-prop-1-en-1-ylphenol; Propenylguaethol
4. **Molecular Formula:** $C_{11}H_{14}O_2$
5. **Molecular Weight:** 178.23
6. **RIFM Number:** 692

2. Physical data

1. **Boiling Point:** >200 °C (Fragrance Materials Association [FMA]), (calculated) 286.55 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA)
3. **Log K_{OW}:** 3.14 (EPI Suite)
4. **Melting Point:** 87 °C (FMA), (calculated) 71.9 °C (EPI Suite)
5. **Water Solubility:** 116.2 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000184 mm Hg @ 20 °C (EPI Suite v4.0), 0.003 mm Hg 20 °C (FMA), 0.000359 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** White or colorless crystalline powder with an intensely sweet, medicinal-phenolic odor.

3. Volume of use (worldwide band)

1. 1–10 metric tons per year@(IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics**: 0.029%@ (RIFM, 2017)
2. **Inhalation Exposure***: 0.00022 mg/kg/day or 0.017 mg/day@ (RIFM, 2017)
3. **Total Systemic Exposure****: 0.00080 mg/kg/day@(RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015, 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, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

1. **Dermal:** 38.4%, read-across from isoeugenol (CAS # 97-54-1)

Liu (1997a): A comparative skin absorption study was conducted on isoeugenol (CAS # 97-54-1). An *in vivo* skin absorption study was conducted in rats. A dose of 2.6 mg/cm^2 of radiolabeled isoeugenol was applied to the skin of 3 F344 rats for 24 h. The absorption through the skin was 36.6 ± 0.6% to 48.7 ± 9.34% of the applied dose. Radioactive urinary metabolites recovered were 25.0 ± 1.0% of the dose. An *in vitro*

skin absorption study was conducted using human skin. Radiolabeled [^{14}C-methoxy] isoeugenol in ethanol was applied to freshly excised human skin at a dose 92.2 μg/cm^2 from 3 volunteers under unoccluded conditions for 72 h in diffusion cells. After 72 h, radioactivity was measured in the skin, on the skin surface, and in the receptor fluid. Recovery of radioactivity as a percent of the dose was 30.0 ± 9.3% in the receptor fluid and 8.4 ± 3.5% in skin. Total uptake was 38.4 ± 12.6%, and the total recovery was 60.1 ± 7.3%. No detectable metabolism was seen in the skin.

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate@(Expert Judgment)

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.1
II*	II	III

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity**: None
   b. **Repeated Dose Toxicity**: Isoeugenol (CAS # 97-54-1)
   c. **Developmental and Reproductive Toxicity**: Isoeugenol (CAS # 97-54-1)
   d. **Skin Sensitization**: None
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity**: None
3. **Read-across Justification**: See Appendix below

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

8. Natural occurrence (discrete chemical) or composition (NCS)

Propenylguaethol is not reported to occur in food 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

Propenylguaethol has been pre-registered for 2010; no dossier available as of 04/15/19.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for propenylguaethol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
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	0.11
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	0.21
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.25
5D	Baby cream, oil, talc	0.071
6	Products with oral and lip exposure	0.58
7	Products applied to the hair with some hand contact	0.32
8	Products with significant ano-genital exposure (tampon)	0.071
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.75
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.75
10B	Aerosol air freshener	3.7
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.071
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	58

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 propenylguaethol, the basis was the reference dose of 0.375 mg/kg/day, a skin absorption value of 38.4%, and a skin sensitization NESIL of 2300 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the currently existing data and use levels, propenylguaethol does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic potential of propenylguaethol was assessed in a bacterial reverse mutation assay conducted equivalent or similar to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 were treated with propenylguaethol with and without an Aroclor 1254-induced rat liver S9 activation system. Propenylguaethol did not produce a significant increase in revertant colonies at concentrations up to 10000 μg/plate in the presence or absence of microsomal activation (Heck, 1989). Under the conditions of this study, propenylguaethol was concluded to be non-mutagenic.

The clastogenic potential of propenylguaethol was assessed in an *in vivo* micronucleus test equivalent or similar to OECD TG 474, where

groups of male and female mice were treated with a single dose (649, 1298, or 1947 mg/kg) of propenylguaethol in olive oil via intraperitoneal injection. Under the conditions of this study, propenylguaethol was considered non-clastogenic (Wild, 1983).

Based on all the available data, propenylguaethol does not present a concern for genotoxic potential.

Additional References: RIFM, 1982; RIFM, 1983; RIFM, 1988a.

Literature Search and Risk Assessment Completed On: 08/12/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. The repeated dose toxicity data on propenylguaethol are insufficient for the repeated dose toxicity endpoint. There are numerous repeated dose studies conducted with read-across material isoeugenol (CAS # 97-54-1; see Section VI). The NOAEL for repeated dose toxicity was determined to be 37.5 mg/kg/day from a gavage 13-week subchronic toxicity study conducted in mice, in which no adverse effects were observed (NTP, 2010 a). When tested at the higher dose of 75 mg/kg/day in a gavage 2-year carcinogenicity study, liver histopathological changes and hepatocarcinogenesis were observed in male mice (NTP, 2010 b). In an *in vitro* skin absorption study conducted using human skin, 38.4% of the applied dosage of isoeugenol was absorbed (Liu, 1997a). **Therefore, the MOE is equal to the isoeugenol NOAEL in mg/kg/day divided by the total systemic exposure, 37.5/0.0008 or 46875.**

The Expert Panel for Fragrance Safety* and FEMA's Expert Panel have reviewed the carcinogenicity data on isoeugenol (Smith, 2009). The US NTP concluded that isoeugenol is hepatocarcinogenic in male mice at 75 mg/kg/day and equivocally carcinogenic in female mice (histiocytic sarcoma) and male rats (thymoma, mammary gland carcinoma) at 300 mg/kg/day (NTP, 2010 b and c). The appearance of male B6C3F1 mouse liver tumors is not relevant to human risk. All dose groups of male B6C3F1 mice suffered chronic hepatic toxicity prior to the development of either liver adenomas or carcinomas, as evidenced by the results of the 90-day and 2-year studies. Hepatocellular adenomas and carcinomas also occurred late in the life span of male mice. Smith et al. (Smith, 2009) reported that the increase in the incidence of tumors in male B6C3F1 mice reflects the impact of high-dose liver damage to an organ already prone to spontaneous development of liver neoplasms (Haseman, 1986, 1990). The total systemic exposure to propenylguaethol is 0.00080 mg/kg/day, which is approximately 9500 times lower than the lowest dose level of isoeugenol in the NTP carcinogenicity studies. The MOE is considered adequate.

11.1.2.1.1. Derivation of reference dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 0.375 mg/kg/day.

The RfD for propenylguaethol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 37.5 mg/kg/day by the uncertainty factor, 100 = 0.375 mg/kg/day.

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

Additional References: RIFM, 1988b; Vollmuth (1989); Schafer (1985); Taylor (1964); RIFM, 2012; RIFM, 2013; Hagan (1967); RIFM, 1954; Bar (1967); Fang (2003); Nishihara (2000); Blair (2000); Fang (2001); Miller (2001); Badger (1999); Badger (2002); Liu (1998); Petridou-Fischer (1987); Fuciarelli (2000); Fuciarelli (2001); Seto (1969); Boutin (1985); Meyer (1959); Meyer (1965); Jimbo (1983a); Jimbo (1983b); Liu (1996); Liu (1997b); Madsen (2011).

Literature Search and Risk Assessment Completed On: 08/10/20.

11.1.3. Developmental and reproductive toxicity

The MOE for propenylguaethol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on propenylguaethol. Read-across material isoeugenol (CAS # 97-54-1; see Section VI) has a gavage developmental toxicity study conducted in rats. The NOAEL for developmental toxicity was determined to be 500 mg/kg/day, based on intrauterine growth retardation and delayed skeletal ossification (George, 2001). These effects occurred at maternally-toxic dosages. In an *in vitro* skin absorption study conducted using human skin, 38.4% of the applied dosage of isoeugenol was absorbed (Liu, 1997a; poster). **Therefore, the MOE for developmental toxicity is equal to the isoeugenol NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.0008 or 625000.**

There are no reproductive toxicity data on propenylguaethol. Read-across material isoeugenol (CAS # 97-54-1) has a gavage multigenerational continuous breeding study conducted in rats. The NOAEL for reproductive toxicity was determined to be 230 mg/kg/day, based on a decreased number of male pups per litter during F0 cohabitation and decreased male and female pup weights during F1 cohabitation (NTP, 2002). In an *in vitro* skin absorption study conducted using human skin, 38.4% of the applied dosage of isoeugenol was absorbed (Liu, 1997a; poster). **Therefore, the MOE for reproductive toxicity is equal to the isoeugenol NOAEL in mg/kg/day divided by the total systemic exposure, 230/0.0008 or 287500.**

Additional References: RIFM, 1988b; Vollmuth (1989); Schafer (1985); Taylor (1964); RIFM, 2012; RIFM, 2013; Hagan (1967); RIFM, 1954; Bar (1967); Fang (2003); Nishihara (2000); Blair (2000); Fang (2001); Miller (2001); Badger (1999); Badger (2002); Liu (1998); Petridou-Fischer (1987); Fuciarelli (2000); Fuciarelli (2001); Seto (1969); Boutin (1985); Meyer (1959); Meyer (1965); Jimbo (1983a); Jimbo (1983b); Liu (1996); Liu (1997b); Madsen (2011).

Literature Search and Risk Assessment Completed On: 08/10/20.

11.1.4. Skin sensitization

Based on the available data, propenylguaethol is considered to be a skin sensitizer with a defined NESIL of 2300 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, propenylguaethol is considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (OECD Toolbox v3.1; Roberts, 2009). In guinea pig sensitization tests, reactions indicative of sensitization were observed (Itoh, 1982; Griepentrog, 1961). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1975). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 2% (2362 μg/cm^2) of propenylguaethol no reactions indicative of sensitization were observed in

Table 1
Data summary for propenylguaethol.

LLNA Weighted Mean EC3 Value [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT[e] (induction) μg/cm^2	NOEL-HMT[e] (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c]
NA[d]	Weak[d]	2362	2772	NA	2300

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.

[c] WoE NESIL = Weight of Evidence No Expected Sensitization Induction Level, 2 significant figures.

[d] No LLNA is available for this material, Hazard classification based on available Guinea pig test method data (Itoh, 1982).

[e] NOEL-HRIPT and NOEL-HMT are Maximum Tested No Observed Effect Levels (MT-NOEL).

any of the 107 volunteers (RIFM, 1991).

The available data demonstrates that propenylguaethol is a skin sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (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. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 0.375 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/24/20.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, propenylguaethol 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 propenylguaethol in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of significant absorbance in the critical range, propenylguaethol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for propenylguaethol were obtained. The spectra indicate minor absorbance in the range of 290–700 nm, under both acidic and neutral conditions. The material could not be analyzed under basic conditions. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/09/18.

11.1.6. Local respiratory toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on propenylguaethol. Based on the Creme RIFM Model, the inhalation exposure is 0.017 mg/day. This exposure is 27.6 times lower than the Cramer Class III* TTC value of 0.47 mg/day based on human lung weight of 650 g (Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/20/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of propenylguaethol 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 Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, propenylguaethol was identified as a fragrance material with the 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 propenylguaethol 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, 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment Section prior to Section 1.

11.2.2. Risk assessment

Based on current (Cramer et al., 1978; IFRA International Fragrance

Association, 2015), propenylguaethol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

Propenylguaethol has been pre-registered for REACH with no additional data at this time.

11.2.4.1. Risk assessment refinement. **Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in µg/L).**

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.14	3.14
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	< **1**	< **1**

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

The RIFM PNEC is 0.209 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 volumes of use.

Literature Search and Risk Assessment Completed On: 03/14/19.

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**
- **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 08/10/20.

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.

	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>24.5</u>			1000000	0.02455	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.186	<u>2.097</u>	8.63	10000	0.209	Phenols
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	13.76	8.686	10.01			Neutral Organics SAR

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111776.

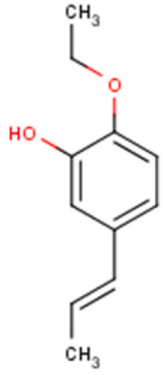
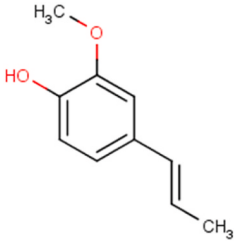
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015) and is consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment or IATA (OECD, 2015) and the European Chemicals Agency (ECHA) read-across assessment framework or RAAF (ECHA, 2016).

- The identified read-across analogs were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and read-across analogs were calculated using EPI Suite v4.11 developed by US EPA (US EPA, 2012a).
- The J_{max} values were calculated using RIFM SAM, and the parameters were calculated using the consensus model (Shen et al., 2014).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox v3.1 (OECD, 2018).
- Developmental toxicity was estimated using CAESAR v2.1.6 (Cassano et al., 2010).
- The major metabolites for the target material and read-across analog were determined and evaluated using OECD QSAR Toolbox v3.1 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Propenylguaethol	Isoeugenol
CAS No.	94-86-0	97-54-1
Structure		
Read-across Endpoint		• Repeated dose toxicity • Developmental and reproductive toxicity
Molecular Formula	$C_{11}H_{14}O_2$	$C_{10}H_{12}O_2$
Molecular Weight	178.23	164.2
Melting Point (°C, EPI Suite)	71.90	61.93
Boiling Point (°C, EPI Suite)	286.55	270.60
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.04786	0.508
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.14	2.65
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	116.2	165.9
J_{max} (μg/cm^2/h, Skin Absorption Model (SAM))	24.898	79.642
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.003586	0.002701
Similarity (Tanimoto Score)		67%
In silico Results for Target and Analog		
Skin Absorption		
Skin Absorption Percentage (SAM)	80%	80%
Repeated Dose Toxicity		
Repeated Dose (HESS)	Not categorized	Not categorized
Developmental and Reproductive Toxicity		
ER Binding (OECD)	Moderate binder, OH group	Weak binder, OH group
Developmental Toxicity Model (CAESAR v2.1.6)	Non-toxicant (moderate reliability)	Non-toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator (OECD)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on propenylguaethol (CAS # 94-86-0). Hence, *in silico* evaluation was conducted to determine a read-across material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, isoeugenol (CAS # 97-54-1) was identified as a read-across material with sufficient toxicological data.

Conclusions

- Isoeugenol (analog) was used as a read-across for propenylguaethol (target material) based on the following:
  - The target material and analog both belong to the generic class of phenols (alkoxyl phenols).
  - Both have the common structural fragments of phenol and propylene.
  - The key differences are that the target material has an ethoxyl group while the analog has a methoxyl group. Also, the propylene fragment is in the *para* position in the target material and the *meta* position in the analog. These differences between the structures do not change the physical–chemical properties or raise any additional structural alerts. Therefore, the toxicity profiles are expected to be similar.
  - The target material and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is a molecular-initiating event analogous to protein binding.
  - The target material and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

Explanation of Cramer Class

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (G.M. Cramer et al., 1978).

- Q1. Normal constituent of the body? No
- Q2. Contains functional groups associated with enhanced toxicity? No
- Q3. Contains elements other than C, H, O, N, divalent S? No
- Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
- Q6. Benzene derivative with certain substituents? No
- Q7. Heterocyclic? No
- Q16. Common terpene? No
- Q17. Readily hydrolyzed to a common terpene? No
- Q19. Open chain? No
- Q23. Aromatic? Yes
- Q27. Rings with substituents? Yes
- Q28. More than one aromatic ring? No
- Q30. Aromatic Ring with complex substituents? Yes
- Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No
- Q32. Contains only the functional groups listed in Q30 or Q31 and those listed below (see Cramer, 1978)? Yes: Class Intermediate (Class II)

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