Food and Chemical Toxicology 149 (2021) 111853

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 2-methoxy-4-propylphenol, CAS Registry Number 2785-87-7

A.M. Api [a], D. Belsito [b], S. Biserta [a], 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], S. Gadhia [a], L. Jones [a], K. Joshi [a], A. Lapczynski [a], M. Lavelle [a], D.C. Liebler [i], M. Na [a], D. O'Brien [a], A. Patel [a], T.M. Penning [j], G. Ritacco [a], F. Rodriguez-Ropero [a], J. Romine [a], N. Sadekar [a], D. Salvito [a], T. W. Schultz [k], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m], S. Tsang [a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, 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, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, 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, 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, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *Member Expert Panel, 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, 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, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

Keywords:
Genotoxicity
Repeated dose
Developmental
And reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

Version: 120619. This version replaces any previous versions.

(*continued on next column*)

(*continued*)

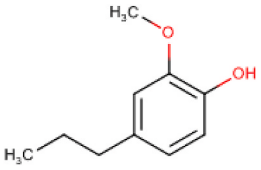
Name: 2-Methoxy-4-propylphenol CAS Registry Number: 2785-87-7

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2020.111853
Received 24 April 2019; Received in revised form 9 October 2020; Accepted 3 November 2020
Available online 7 November 2020

(*continued*)



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
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
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
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.

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

2-Methoxy-4-propylphenol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog guaiacol (CAS # 90-05-1) show that 2-methoxy-4-propylphenol is not expected to be genotoxic. Data on read-across material eugenol (CAS # 97-53-0) provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity endpoint. The developmental and reproductive toxicity and the local respiratory toxicity endpoints were evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material; the exposure to 2-methoxy-4-propylphenol is below the TTC (1.4 mg/day). Data provided 2-methoxy-4-propylphenol a No Expected Sensitization Induction Level (NESIL) of 1700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet (UV) spectra; 2-methoxy-4-propylphenol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-methoxy-4-propylphenol 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 in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(Pool, 1982; Sekizawa, 1982; Shelby, 1993)
Repeated Dose Toxicity: NOAEL = 300 mg/kg/day.	NTP (1983)
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: NESIL = 1700 μg/cm^2	(Gerberick, 2005; Roberts, 2007; RIFM, 2015)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB; RIFM, 1988)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.7 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 36.21 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 2.804 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: 2.804 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.2804 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** 2-Methoxy-4-propylphenol
2. **CAS Registry Number:** 2785-87-7
3. **Synonyms:** Dihydroeugenol; Phenol, 2-methoxy-4-propyl-; 4-Propylguaicol; 5-Propyl-ortho-hydroxyanisole; 4-Propyl-ortho-methoxyphenol; o-ﾒﾄｷｼｱﾙｷﾙ(C1 ~ 3)ﾌｪﾉｰﾙ; 2-ﾒﾄｷｼ-4-ﾌﾟﾛﾋﾟﾙﾌｪﾉｰﾙ; 2-ﾒﾄｷｼ-4-□ﾌﾟﾛﾋﾟﾙﾌｪﾉｰﾙ; 2-Methoxy-4-propylphenol
4. **Molecular Formula:** $C_{10}H_{14}O_2$
5. **Molecular** Weight**:** 166.22
6. **RIFM Number:** 1011
7. Stereochemistry: Isomer not specified. No isomerism center present and no isomers possible.

2. Physical data

1. **Boiling Point:** 250 °C (Fragrance Materials Association [FMA] Database) 265.51 °C (EPI Suite, calculated)
2. **Flash Point:** >200 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.88 (Smith, 2002), 2.87 (EPI Suite)
4. **Melting Point**: 61.64 °C (EPI Suite)
5. **Water Solubility:** 228 mg/L (EPI Suite)
6. **Specific Gravity:** 1.040 (FMA Database)

7. **Vapor Pressure:** 0.00114 mm Hg at 20 °C (EPI Suite v4.0), 0.003 mm Hg at 20 °C (FMA Database), 0.00213 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar extinction coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1}).
9. **Appearance/Organoleptic:** Colorless oily liquid with a warm, spicy, sweet, and slightly balsamic odor

3. Exposure

1. **Volume of Use (**worldwide **band):** 10–100 metric tons per year (IFRA, 2015)
2. **95**th **Percentile** Concentration **in Hydroalcoholics:** 0.089% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00043 mg/kg/day or 0.033 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00087 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 IV. 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).

4. Derivation of systemic absorption

1. **Dermal:** 22.6%

Liu (1997a): A comparative skin absorption study was conducted. An *in vivo* skin absorption study was conducted in rats. A dose of 2.6 mg/cm^2 of radiolabeled read-across material eugenol (CAS # 97-53-0; see Section V) was applied to the skin of 3 F344 rats for 24 h. The absorption through the skin was 35.9 ± 6.4–39.4 ± 9.0% of the dose. Radioactive urinary metabolites recovered were 27.2 ± 6.8%. An *in vitro* skin absorption study was conducted using human skin. Radiolabeled eugenol in ethanol was applied to freshly excised human skin at a dose 48.2 μg/cm^2 from 3 volunteers under unoccluded conditions for 72 h in diffusion cells. The mean absorption through the skin was 18.5 ± 1.5% of the applied dose, while 4.1 ± 0.4% remained in the skin. The total uptake was 22.6 ± 1.2%, while the total recovery was 34.5 ± 7%.

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

5. Computational toxicology evaluation

1. **Cramer** Classification**:** Class I, Low

Expert Judgment	Toxtree v.2.6	OECD QSAR Toolbox v.3.1
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Guaiacol (CAS # 90-05-1)
   b. **Repeated Dose Toxicity:** Eugenol (CAS # 97-53-0)
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

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

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

2-Methoxy-4-propylphenol is reported to occur in the following foods by the VCF*:

Acerola (*Malpighia*)	Katsuobushi (dried bonito)
Cuttlefish	Mate (*Ilex paraguayensis*)
Fish	Mushroom
Grape brandy	Pear brandy
Pork	Tea
Rhubarb	Truffle
Rum	Whisky
Salami	Wine
Sugar molasses	

*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.

8. REACH dossier

Available; accessed 03/15/19 (ECHA, 2017).

9. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-methoxy-4-propylphenol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.13
2	Products applied to the axillae	0.039
3	Products applied to the face/body using fingertips	0.78
4	Products related to fine fragrances	0.73
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.19
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.19
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.19
5D	Baby cream, oil, talc	0.062
6	Products with oral and lip exposure	0.43
7	Products applied to the hair with some hand contact	1.5
8	Products with significant ano-genital exposure (tampon)	0.062
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.4
10B	Aerosol air freshener	5.1
11		0.062

(*continued on next page*)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 2-methoxy-4-propylphenol, the basis was the reference dose of 3.00 mg/kg/day, a skin absorption value of 22.6%, and a skin sensitization NESIL of 1700 μg/cm^2. [b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 2-methoxy-4-propylphenol does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of 2-methoxy-4-propylphenol; however, read-across can be made to guaiacol (CAS # 90-05-1; see Section V). The mutagenic activity of guaiacol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with guaiacol in dimethyl sulfoxide (DMSO) at concentrations up to 10,000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Haworth, 1983). Under the conditions of the study, guaiacol was not mutagenic in the Ames test.

The clastogenic activity of guaiacol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female NMRI mice. Doses of 125, 250, and 500 mg/kg body weight were administered. Mice from each dose level were euthanized at 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011; accessed 05/18/18). Under the conditions of the study, guaiacol was considered not to be clastogenic in the *in vivo* micronucleus test.

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

Additional References: Florin (1980); Nestmann (1980); Stich (1981); Pool (1982); Nestmann (1983); Rapson (1980); Haworth (1983); Douglas (1980); Jansson (1986); Ferretti (1977); Tsutsui (1987); Ohshima (1989); Aeschbacher (1989); Rosin (1984); Levan (1948); Hikiba (2005); Miyachi (2005); Hamaguchi (2000); Someya (2008).

Literature Search and Risk Assessment Completed On: 05/18/18.

10.1.2. Repeated dose toxicity

The margin of exposure for 2-methoxy-4-propylphenol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. The repeated dose toxicity data on 2-methoxy-4-propylphenol are insufficient for the repeated dose toxicity endpoint. Read-across material eugenol (CAS # 97-53-0; see Section V) has numerous repeated dose toxicity studies. The NOAEL for repeated dose toxicity was determined to be 300 mg/kg/day from a dietary 13-week subchronic toxicity study conducted in rats, based on reduced body weights (NTP, 1983). **Therefore, the MOE is equal to the eugenol NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.00087 or 344828.**

The Expert Panel for Fragrance Safety* has reviewed the carcinogenicity data on eugenol. The US NTP concluded that hepatocellular tumors observed following eugenol administration were considered to be associated with the dietary administration of eugenol, but because of the lack of a dose-response effect in male mice and the marginal combined increases in female mice, there was equivocal evidence of carcinogenicity (NTP, 1983). It was not carcinogenic to rats (NTP, 1983). Hepatotoxicity might have played a role in the development of the hepatic tumors in B6C3F1 mice, which are sensitive for the development of liver tumors by non-genotoxic mechanisms. The total systemic exposure to 2-methoxy-4-propylphenol is 0.00087 mg/kg/day, which is nearly ~52,000 times lower than the lowest dose level of eugenol in the mouse NTP study. This MOE is considered adequate.

Section IX 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, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 3.0 mg/kg/day.

The RfD for 2-methoxy-4-propylphenol was calculated by dividing the NOAEL of 300 mg/kg/day by the uncertainty factor, 100 = 3.0 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: Caujolle and Meynier, 1960; Petridou--Fischer, 1987; Jimbo, 1983; Vishteh, 1986; Taylor, 1964; Breidenbach, 1952; Boonchird and Flegel, 1982; Lauber, 1950; Cambel, 1952; Rompelberg, 1995a; Hirose, 1987; Hagan, 1965; Hagan, 1967; Rompelberg, 1995b; Ward, 1989; RIFM, 1958; RIFM, 1954; Bar, 1967; Van Duuren and Goldschmidt, 1976; Van Duuren et al., 1966; Miller, 1983; Koujitani, 2001; Hitchcock, 1952; Amini, 2002; Howes, 2002; Blair, 200; Nishihara, 2000; Fischer, 1990b; Sutton, 1986; Caldwell, 1985; Delaforge, 1980; Weinberg, 1972; Delaforge, 1976; Green and Tephl, 1996; Thompson, 1989; Meredith, 2009; Boutin, 1981; Boutin, 1985; Thompson, 1990; Delaforge, 1978; Boutin, 1984; Leclerc, 2002; Swanson, 1981; Dahl and Hadley, 1983; Golberg, 1978; Thompson, 1991; Gardner, 1995; Sutton, 1985; Swanson, 1978; Fischer, 1990a; Laekeman, 1990; Schroder, 1932; Thompson, 1998; Meyer, 1959; Meyer, 1965; Liu, 1996; ProcterGamble, 1996; Liu, 1997b; Hotchkiss, 1998; Zhao, 1998; Schmitt, 2009; Schmitt, 2010.

Literature Search and Risk Assessment Completed On: 05/10/18.

10.1.3. Developmental and Reproductive Toxicity

There are insufficient developmental or reproductive data on 2-methoxy-4-propylphenol or any read-across materials. The exposure is below the Threshold of Toxicological Concern (TTC).

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on 2-methoxy-4-propylphenol or any read-across material that can be used to support the developmental or reproductive toxicity endpoints. When correcting for skin absorption (see Section IV), the total systemic exposure (0.87 μg/kg/day) is below the TTC for 2-methoxy-4-propylphenol (30 μg/kg bw/day).

Additional References: Caujolle and Meynier, 1960; Petridou--Fischer et al., 1987; Jimbo, 1983; Vishteh et al., 1986; Taylor et al., 1964; Breidenbach et al., 1952; Boonchird and Flegel, 1982; Lauber and Hollander, 1950; Cambel and Conroy, 1952; Rompelberg et al., 1995a; Hirose et al., 1987; Hagan et al., 1965; Hagan et al., 1967; Rompelberg et al., 1995b; Ward et al., 1989; RIFM, 1958; RIFM, 1954; Bar and Griepentrog, 1967; Van Duuren and Goldschmidt, 1976; Van Duuren et al., 1966; Miller et al., 1983; Koujitani et al., 2001; Hitchcock, 1952; Amini et al., 2002; Howes et al., 2002; Blair et al., 2000; Nishihara et al., 2000; Fischer et al., 1990b; Sutton, 1986; Caldwell et al., 1985; Delaforge et al., 1980; Weinberg et al., 1972; Delaforge et al., 1976; Green and Tephl, 1996; Thompson et al., 1989; Meredith et al., 2009; Boutin et al., 1981; Boutin et al., 1985; Thompson et al., 1990; Delaforge et al., 1978; Boutin et al., 1984; Leclerc et al., 2002; Swanson et al., 1981; Dahl and Hadley, 1983; Golberg, 1978; Thompson et al., 1991; Gardner et al., 1995; Sutton et al., 1985; Swanson et al., 1978; Fischer and Dengler, 1990a; Laekeman et al., 1990; Schroder and Vollmer, 1932; Thompson et al., 1998; Meyer and Meyer, 1959; Meyer, 1965; Liu and Hotchkiss, 1996; Procter and Gamble Company, 1996; Liu and Hotchkiss, 1997b; Hotchkiss, 1998; Zhao and Singh, 1998; Schmitt et al., 2009; Schmitt et al., 2010.

Literature Search and Risk Assessment Completed On: 10/18/13.

10.1.4. Skin Sensitization

Based on the available data for 2-methoxy-4-propylphenol is considered to be a weak skin sensitizer with a NESIL of 1700 μg/cm^2.

10.1.4.1. Risk assessment. Based on the available data, 2-methoxy-4-propylphenol is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.5.0). In a murine local lymph node assay (LLNA), 2-methoxy-4-propylphenol was found to be sensitizing with an EC3 value of 6.8% (1700 μg/cm^2) (Gerberick et al., 2005; Roberts et al., 2007). In guinea pig maximization tests, 2-methoxy-4--propylphenol presented reactions indicative of sensitization at 100%. (RIFM, 1988). However, in a guinea pig closed epicutaneous test (CET), no reactions indicative of sensitization were observed (Itoh, 1982). In a human maximization test, no skin sensitization reactions were observed with 2-methoxy-4-prpopylphenol at 8% (5520 μg/cm^2) (Kligman, 1977). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 1.5% or 1771 μg/cm^2 of 2-methoxy-4-propylphenol in 1:3 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 107 volunteers (RIFM, 2015).

Based on the available animal and human data 2-methoxy-4-propylphenol is considered a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 1700 μg/cm^2 (Table 1). Section IX 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, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of3.0 mg/kg/day).

Additional References: Itoh, 1982.

Literature Search and Risk Assessment Completed On: 10/19/15.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis spectra and the available data, 2-methoxy-4-propylphenol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. 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 et al., 2009). In a phototoxicity study in guinea pigs, application of 10% 2-methoxy-4-propylphenol did not result in responses indicative of photoallergy or phototoxicity (RIFM, 1988). Based on the lack of significant absorbance in the critical range and the available *in vivo* data, 2-methoxy-4-propylphenol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 2-methoxy-4-propylphenol were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, 1000 L mol^{-1} · cm^{-1}, of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/11/18.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2-methoxy-4-propylphenyl is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2-methoxy-4-propylphenyl. Based on the Creme RIFM Model, the inhalation exposure is 0.033 mg/day. This exposure is 42.42 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: 06/08/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-methoxy-4-propylpheol 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

Table 1
Data summary for 2-methoxy-4-propylphenol.

local Lymph Node Assay (LLNA) Weighted Mean EC3 Value (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c]
1700 [1]	Weak	1772	5520	NA	1700

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 limited to 2 significant figures.

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, 2-methoxy -4-propylpheol 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 v4.1 (US EPA, 2012a) did not identify 2-methoxy-4-propylpheol as possibly 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 v4.1).

10.2.2. Risk assessment

Based on current VoU (IFRA, 2015), 2-methoxy-4-propylpheol presents a risk to the aquatic compartment.

10.2.2.1. Key studies. ***Biodegradation:*** No data available.

Ecotoxicity: No data available.

10.2.2.2. Other available data. 2-Methoxy -4-propylpheol has been pre-registered for REACH with no additional data at this time.

Ecotoxicity: No data available.

10.2.3. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.87	2.87
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
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 0.2804 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: 05/02/18.

11. 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	39.24			1,000,000	0.0392	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	6.329	2.804	11.85 L	10,000	0.2804	Phenols
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	22.72	13.97	14.49			Neutral Organics

- **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 01/22/19.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111853.

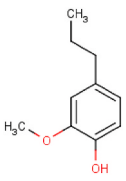
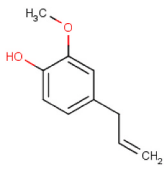
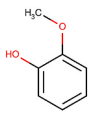
Appendix

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, 2016).

- 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 substance and the read-across analogs were calculated using EPI Suite v4.11 (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 v3.4 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	2-Methoxy-4-propylphenol	Eugenol	Guaiacol
CAS No.	2785-87-7	97-53-0	90-05-1
Structure			
Similarity (Tanimoto Score)		0.7	0.41
Read-across Endpoint		• Repeated Dose	• Genotoxicity
Molecular Formula	$C_{10}H_{14}O_2$	$C_{10}H_{14}O_2$	$C_7H_8O_2$
Molecular Weight	166.22	164.21	124.13
Melting Point (°C, EPI Suite)	61.64	60.57	32
Boiling Point (°C, EPI Suite)	265.51	264.26	205
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.00213	0.00948	0.113
	228	754	7226

(continued on next page)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)			
Log KOW	2.87	2.73	1.32
J_{max} (μg/cm^2/h, SAM)	12.17	81.29	266.39
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.006535	0.00487	1.22E-001
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found		• No alert found
DNA Binding (OECD QSAR Toolbox v3.4)	• Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals		• Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals
Carcinogenicity (ISS)	• No alert found		• 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	• Phenol Type Compounds		• Phenol Type Compounds
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 2-methoxy-4-propylphenol (CAS # 2785-87-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, eugenol and guiacol were identified as a read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Eugenol (CAS # 97-53-0) was used as a read-across analog for the target material 2-methoxy-4-propylphenol (CAS # 2785-87-7) for the repeated dose toxicity endpoint.
  - o The target and analog both belong to the generic class of phenols, specifically 2-methoxy substituted phenols.
  - o Both have a common structural fragment of 2-methoxyl phenol and a branch chain in the *para* position.
  - o The key difference is that the target has an alkyl branch chain, whereas the analog has propene substitution with a vinyl bond. This structural difference is predicted to increase the reactivity of the read-across analog compared to the target substance.
  - o The target substance 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.
- Guaiacol (CAS # 90-05-1) was used as a read-across analog for the target material 2-methoxy-4-propylphenol (CAS # 2785-87-7) for the genotoxicity endpoint.
  - o The target and analog both belong to the generic class of phenols, specifically 2-methoxy substituted phenols.
  - o Both have a common structural fragment of 2-methoxyl phenol.
  - o The key difference is that the target has an alkyl branch chain in the *para* position, whereas the analog has no substituents. This structural difference is predicted to increase the reactivity of the read-across analog compared to the target substance.
  - o The target substance and the read-across analog are predicted to show DNA binding via Michael addition up on P450 mediated metabolic transformation to Quinones. Both of the substances are also predicted to show mutagenicity as they have a 1–3 hydrogen bond acceptor substructure. The data described in the genotoxicity section confirm that the read-across analog does not pose a concern for genetic toxicity. Therefore, based on structural similarity and the data for read-across analog, the alerts are superseded by data.
  - o The target substance 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

Aeschbacher, H.U., Wolleb, U., Loliger, J., Spadone, J.C., Liardon, R., 1989. Contribution of coffee aroma constituents to the mutagenicity of coffee. Food Chem. Toxicol. 27 (4), 227–232.

Amini, A., Cheraghi, E., Safaee, M.R., Hill, M., 2002. The role of eugenol in the reduction of teratogenic effects of retinoic acid on skeletal morphology of mice embryo. Yakhten 4 (16), 195–200.

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.

Bar, V.F., Griepentrog, F., 1967. Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel Fur Lebensmittel. (Where we stand concerning the evaluation of flavoring substances from the viewpoint of health). Medizin Ernahr 8, 244–251.

Blair, R.M., Fang, H., Branham, W.S., Hass, B.S., Dial, S.L., Moland, C.L., Tong, W., Shi, L., Perkins, R., Sheehan, D.M., 2000. The estrogen receptor relative binding affinities of 188 natural and xenochemicals: structural diversity of ligands. Toxicol. Sci. 54 (1), 138–153.

Boonchird, C., Flegel, T.W., 1982. In vitro antifungal activity of eugenol and vanillin against candida albicans and cryptococcus neoformans. Can. J. Microbiol. 28 (11), 1235–1241.

Boutin, J.A., Lepage, C., Batt, A.M., Siest, G., 1981. The activity of hepatic UDP-glucuronosyltransferase from control and induced pigs toward 17 hydroxylated aglycones. IRCS med. Sci. IRCS Medical Science 9, 633–634.

Boutin, J.A., Thomassin, J., Siest, G., Batt, A.M., 1984. Inhibition studies of microsomal UDP-glucuronosyltransferase activities by furosemide and salicylamide. Pharmacol. Res. Commun. 16 (3), 227–241.

Boutin, J.A., Thomassin, J., Siest, G., Cartier, A., 1985. Heterogeneity of hepatic microsomal UDP-glucuronosyltransferase activities. Conjugations of phenolic and monoterpenoid aglycons in control and induced rats and Guinea pigs. Biochem. Pharmacol. 34 (13), 2235–2249.

Breidenbach, A.W., Cambel, P., Ray, F.E., 1952. Gastric ascorbic acid in the gastritic rat. PSEBM (Proc. Soc. Exp. Biol. Med.) 80, 144–146.

Caldwell, J., Farmer, P.B., Sangster, S.A., Sutton, J.D., 1985. The fate of eugenol in the rat and its variation with dose. Br. J. Pharmacol. 84, 24P.

Cambel, P., Conroy, C., 1952. Ectopic pancreatic tissue in the stomach wall of an albino rat. Q. J. Fla. Acad. Sci. 15, 147–148.
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.
Caujolle, F., Meynier, D., 1960. Pharmacodynamics - toxicity of methyl eugenol, methyl isoeugenols, and of methyl dihydroeugenol. Compt. Rend. 250, 1148–1149.
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.
Dahl, A.R., Hadley, W.M., 1983. Formaldehyde production promoted by rat nasal cytochrome P-450-dependent monooxygenases with nasal decongestants, essences, solvents, air pollutants, nicotine, and cocaine as substrates. Toxicol. Appl. Pharmacol. 67 (2), 200–205.
Delaforge, M., Janiaud, P., Chessebeuf, M., Padieu, P., Maume, B.F., 1976. Possible occurrence of the epoxide-diol metabolic pathway for hepatocarcinogenic safrole in cultured rat liver cells, as compared with whole animal: a MetabolicStudy by mass spectrometry. Adv. in Mass Spec. in Bioch. & Med. 2, 65–89.
Delaforge, M., Janiaud, P., Levi, P., Morizot, J.P., 1980. Biotransformation of allylbenzene analogues in vivo and in vitro through the epoxide-diol pathway. Xenobiotica 10 (10), 737–744.
Delaforge, M., Janiaud, P., Maume, B.F., Padieu, P., 1978. Direct evidence of epoxide metabolic pathway for natural allylbenzene compounds in adult rat liver cell culture. Rec. Dev. Mass Spectr. Biochem. Med. 1, 521–539.
Douglas, G.R., Nestmann, E.R., Betts, J.L., Mueller, J.C., Lee, E.G.-H., Stich, H.F., San, R. H.C., Brouzes, R.J.P., Chmelauskas, A., Paavila, H.D., Walden, C.C., 1980. Mutagenic activity in pulp mill effluents. In: Water Chlorination. Env. Impact & Health Effects, vol. 3, pp. 865–880. Ch. 76.
ECHA, 2011. Guaiacol registration dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/9979/1.
ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.
ECHA, 2016. Read-across assessment framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.
Ferretti, J.J., Lu, W., Liu, M.-B., 1977. Mutagenicity of benzidine and related compounds employed in the detection of hemoglobin. Am. J. Clin. Pathol. 67, 526–527.
Fischer, I.U., Dengler, H.J., 1990. Sensitive high-performance liquid chromatographic assay for the determination of eugenol in body fluids. J. Chromatogr. A 525, 369–377.
Fischer, I.U., vonUnruh, G.E., Dengler, H.J., 1990. The metabolism of eugenol in man. Xenobiotica 20 (2), 209–222.
Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames Test. Toxicology 18 (3), 219–232.
Gardner, I., Bergin, P., Stening, P., Kenna, J.G., Caldwell, J., 1995. Protein adducts derived from methyleugenol. ISSX International Meeting 4th (8), 208.
Gerberick, G.F., Ryan, C.A., Kern, P.S., Schlatter, H., Dearman, R.J., Kimber, I., Patlewicz, G.Y., Basketter, D.A., 2005. Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods. Dermatitis 16 (4), 157–202.
Golberg, L., 1978. Cell metabolism of safrole, isosafrole and eugenol [Editorial]. Food Chem. Toxicol. 16, 294.
Green, M.D., Tephly, T.R., 1996. Glucuronidation of amines and hydroxylated xenobiotics and endobiotics catalyzed by expressed human UGT1.4 protein. Drug Metabol. Dispos. 24 (3), 356–363.
Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.M., Brouwer, J.B., 1967. Food flavorings and compounds of related structure. II. Subacute and chronic toxicity. Food Chem. Toxicol. 5 (2), 141–157.
Hagan, E.C., Jenner, P.M., Jones, W.I., Fitzhugh, O.G., Long, E.L., Brouwer, J.G., Webb, W.K., 1965. Toxic properties of compounds related to safrole. Toxicol. Appl. Pharmacol. 7 (1), 18–24.
Hamaguchi, F., Tsutsui, T., 2000. Assessment of genotoxicity of dental antiseptics: ability of phenol, guaiacol, p-phenolsulfonic acid, sodium hypochlorite, p-chlorophenol, m-cresol or formaldehyde to induce unscheduled DNA synthesis in cultured Syrian hamster embryo cells. Jpn. J. Pharmacol. 83 (3), 273–276.
Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., Zeiger, E., 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. 5 (Suppl. 1), 3–142.
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.
Hikiba, H., Watanabe, E., Barrett, J.C., Tsutsui, T., 2005. Ability of fourteen chemical agents used in dental practice to induce chromosome aberrations in Syrian hamster embryo cells. J. Pharmacol. Sci. 97 (1), 146–152.
Hirose, M., Masuda, A., Imaida, K., Kagawa, M., Tsuda, H., Ito, N., 1987. Induction of forestomach lesions in rats by oral administrations of naturally occurring antioxidants for 4 weeks. Jpn. J. Canc. Res. 78, 317–321.
Hitchcock, C.R., 1952. Failure of eugenol and heat to potentiate gastric tumor induction by 20-methylcholanthrene in mice. J. Natl. Cancer Inst. 12 (4), 723–733.
Hotchkiss, S.A.M., 1998. Absorption of fragrance ingredients using in vitro models with human skin. Fragrances: Beneficial and Adverse Effects 125–135.
Howes, M.-J.R., Houghton, P.J., Barlow, D.J., Pocock, V.J., Milligan, S.R., 2002. Assessment of estrogenic activity in some common essential oil constituents. J. Pharm. Pharmacol. 54 (11), 1521–1528.
IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.
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.
Jansson, T., Curvall, M., Hedin, A., Enzell, C.R., 1986. In vitro studies of biological effects of cigarette smoke condensate. II. Induction of sister-chromatid exchanges in human lymphocytes by weakly acidic, semivolatile constituents. Mutat. Res. Genet. Toxicol. 169 (3), 129–139.
Jimbo, Y., 1983. Penetration of fragrance compounds through human epidermis. J. Dermatol. (Tokyo) 10 (3), 229–239.
Kligman, A.M., 1977. Report on Human Maximization Studies. Unpublished Report to RIFM.
Koujitani, T., Yasuhara, K., Tamura, T., Onodera, H., Takagi, H., Takizawa, T., Hirose, M., Hayashi, Y., Mitsumori, K., 2001. Lack of modifying effects of eugenol on development of lung proliferative lesions induced by urethane in transgenic mice carrying the human prototype c-Ha-ras gene. J. Toxicol. Sci. 26 (3), 129–139.
Laekeman, G.M., VanHoof, L., Haemers, A., Vanden Berghe, D.A., Herman, A.G., Vlietinck, A.J., 1990. Eugenol a valuable compound for in vitro experimental research and worthwhile for further in vivo investigation. Phytother Res. 493, 90–96.
Lauber, F.U., Hollander, F., 1950. Toxicity of the mucigogue, eugenol, administered by stomach tubes to dogs. Gastroenterology 15 (3), 481–486.
Leclerc, S., Heydel, J.-M., Amosse, V., Gradinaru, D., Cattarelli, M., Artur, Y., Goudonnet, H., Magdalou, J., Netter, P., Pelczar, H., Minn, A., 2002. Glucuronidation of odorant molecules in the rat olfactory system. Activity, expression and age-linked modification of UDP-glucuronosyltransferase isoforms, UGT1A6 and UGT2A1, and relation to mitral cell activity. Mol. Brain Res. 107 (2), 201–213.
Levan, A., Tjio, J.H., 1948. Induction of chromosome fragmentation by phenols. Hereditas 34, 453–484.
Liu, F.C., Hotchkiss, S.A.M., 1996. In Vitro Percutaneous Disposition of the Cutaneous Sensitizers Eugenol and Isoeugenol. Presented at the European Society of Contact Dermatitis/Jadassohn Centenary Congress. London.
Liu, F.C., Hotchkiss, S.A.M., 1997a. Comparative disposition of the cutaneous sensitizers eugenol and isoeugenol in rat and human skin. Hum. Exp. Toxicol. 16 (1), 50.
Liu, F.C., Hotchkiss, S.A.M., 1997b. Comparative Skin Absorption, Metabolism and Protein Binding of the Sensitizers Eugenol and Isoeugenol (Unpublished. Presented at Eur. Res. Gp. on Exptl. Contact Dermatitis in Odense).
Meredith, C., Massey, E., Minet, E., 2009. In vitro characterization of hepatic eugenol and methyleugenol bioactivation versus detoxification pathways. Toxicologist 108 (1), 55.
Meyer, F., Meyer, E., 1959. Absorption of ethereal oils and substances contained in them through the skin. Arzneimittel-Forschung [Drug Research]. Arzneim. Forsch. 9, 516–519.
Meyer, F., 1965. Penetrating Agents. Patent. British, 1,001,949, M49750IVa/30h, 7/20/61.
Miller, E.C., Swanson, A.B., Phillips, D.H., Fletcher, T.L., Liem, A., Miller, J.A., 1983. Structure-activity studies of the carcinogenicities in the mouse and rat of some naturally occurring and synthetic alkenylbenzene derivatives related to safrole and estragole. Canc. Res. 43 (3), 1124–1134.
Miyachi, T., Tsutsui, T., 2005. Ability of 13 chemical agents used in dental practice to induce sister-chromatid exchanges in Syrian hamster embryo cells. odontology/the society of the Nippon Dental University. Odontology 93 (1), 24–29.
National Toxicology Program, 1983. Carcinogenesis Studies of Eugenol in F344/N Rats and B6C3F1 Mice (Feed Studies). NTP-TR-223. Unpublished.
Nestmann, E.R., Lee, E.G.-H., 1983. Mutagenicity of constituents of pulp and paper mill effluent in growing cells of saccharomyces cerevisiae. Mutat. Res. Lett. 119 (3–4), 273–280.
Nestmann, E.R., Lee, E.G.-H., Matula, T.I., Douglas, G.R., Mueller, J.C., 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the salmonella/mammalian-microsome assay. Mutat. Res. Genet. Toxicol. 79 (3), 203–212.
Nishihara, T., Nishikawa, J., Kanayama, T., Dakeyama, F., Saito, K., Imagawa, M., Takatori, S., Kitagawa, Y., Hori, S., Utsumi, H., 2000. Estrogenic activities of 517 chemicals by yeast two-hybrid assay. J. Health Sci. 46 (4), 282–298. Journal of Health Sciences.
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/.
Ohshima, H., Friesen, M., Malaveille, C., Brouet, I., Hautefeuille, A., Bartsch, H., 1989. Formation of direct-acting genotoxic substances in nitrosated smoked fish and meat products: identification of simple phenolic precursors and phenyldiazonium ions as reactive products. Food Chem. Toxicol. 27 (3), 193–203.
Petridou-Fischer, J., Whaley, S.L., Dahl, A.R., 1987. In vivo metabolism of nasally instilled dihydrosafrole [1-(3,4-methylenedioxyphenyl)propane] in dogs and monkeys. Chem. Biol. International Rep. 64, 1–12.
Pool, B.L., Lin, P.Z., 1982. Mutagenicity testing in the Salmonella typhimurium assay of phenolic compounds and phenolic fractions obtained from smokehouse smoke condensates. Food Chem. Toxicol. 20 (4), 383–391.

Procter, Gamble Company, 1996. [Submission to EPA] Dermal Penetration Potential of Perfume Materials, with Letter Dated 5/28/96. Unpublished.
Rapson, W.H., Nazar, M.A., Butsky, V.V., 1980. Mutagenicity produced by aqueous chlorination of organic compounds. Bull. Environ. Contam. Toxicol. 24 (4), 590–596.
RIFM (Research Institute for Fragrance Materials, Inc), 1954. Pathological Changes in Rats from Feeding of Various Flavoring Agents. Private Communication to FEMA. Unpublished report from Food and Drug Administration. RIFM report number 4850. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1958. Toxicolgical Screening of Eugenol, P-Methoxybenzaldehyde and Piperonal in Rats. Class IX. Aromatic Aldehydes. Unpublished report from Trubek Laboratories, Inc. RIFM report number 29143. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1988. Guinea Pig Photoallergy Test with 2-Methoxy-4-Propylphenol (Dihydroeugenol). Unpublished report from Quest International. RIFM report number 45906. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. RIFM Report Number 55663. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015. Repeat Insult Patch Test with 2-Methoxy-4-Propylphenol. RIFM Report Number 69224. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2017. Exposure Survey 14. January 2017.
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.
Rompelberg, C.J.M., Steenwinkel, M.J.S.T., vanAsten, J.G., vanDelft, J.H.M., Baan, R.A., Verhagen, H., 1995a. Effect of eugenol on the mutagenicity of benzo[alpha]Pyrene and the formation of benzo[alpha]Pyrene-DNA adducts in the lambda-LACZ-transgenic mouse. In: Modulation of Biotransformation and Genotoxicity by Eugenol, pp. 99–116 (Chapter 6).
Rompelberg, C.J.M., Vogels, J.T.W.E., DeVogel, N., Bruijntjes-Rozier, G.C.D.M., Stenhuis, W.H., Bogaards, J.J.P., Verhagen, H., 1995b. Effect of short-term dietary administration of eugenol in humans. In: Modulation of Biotransformation and Genotoxicity by Eugenol. Chapter 7, pp. 117–130.
Rosin, M.P., 1984. The influence of pH on the convertogenic activity of plant phenolics. Mutation Research. Genetic Toxicology 135 (1), 109–113.
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.
Schmitt, S., Schaefer, U., Sporer, F., Reichling, J., 2010. Comparative study on the in vitro human skin permeation of monoterpenes and phenylpropanoids applied in rose oil and in form of neat single compounds. Pharmazie 65 (2), 102–105.
Schmitt, S., Schaefer, U.F., Doebler, L., Reichling, J., 2009. Cooperative interaction of monoterpenes and phenylpropanoids on the in vitro human skin permeation of complex composed essential oils. Planta Med. 75 (13), 1381–1385.
Schroder, V., Vollmer, H., 1932. The excretion of thymol, carvacrol, eugenol and guiacol and the distribution of these substances in the organism. Archives of exp. Path. Pharmak. 168, 331–353.
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.
Sekizawa, J., Shibamoto, T., 1982. Genotoxicity of safrole-related chemicals in microbial test systems. Mutat. Res. Genet. Toxicol. 101 (2), 127–140.
Shelby, M.D., Erexson, G.L., Hook, G.L., Tice, R.R., 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. Environ. Mol. Mutagen. 21 (2), 160–179.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Smith, C.J., Perfetti, T.A., Morton, M.J., Rodgman, A., Garg, R., Selassie, C.D., Hansch, C., 2002. The relative toxicity of substituted phenols reported in cigarette mainstream smoke. Toxicol. Sci. 69 (1), 265–278.
Someya, H., Higo, Y., Ohno, M., Tsutsui, T.W., Tsutsui, T., 2008. Clastogenic activity of seven endodontic medications used in dental practice in human dental pulp cells. Mutat. Res. Genet. Toxicol. Environ. Mutagen 650 (1), 39–47.
Stich, H.F., Rosin, M.P., Wu, C.H., Powrie, W.D., 1981. The action of transition metals on the genotoxicity of simple phenols, phenolic acids and cinnamic acids. Canc. Lett. 14 (3), 251–260.
Sutton, J.D., 1986. Doctorial Dissertation: Metabolic Studies of Eugenol in Relation to its Safety Evaluation (Unpublished. A thesis submitted for the degree of Doctor of Philosophy in the University of London).
Sutton, J.D., Sangster, S.A., Caldwell, J., 1985. Dose-dependent variation in the disposition of eugenol in the rat. Biochem. Pharmacol. 34 (3), 465–466.
Swanson, A.B., Miller, E.C., Miller, J.A., 1978. Metabolism of naturally occurring arylalkenes to mutagenic epoxides. Federation Proceedings Abstracts 37 (6), 1383.
Swanson, A.B., Miller, E.C., Miller, J.A., 1981. The side-chain epoxidation and hydroxylation of the hepatocarcinogens safrole and estragole and some related compounds by rat and mouse liver microsomes. Biochemica et Biophysica Acta 673 (4), 504–516.
Taylor, J.M., Jenner, P.M., Jones, W.I., 1964. A comparison of the toxicity of some allyl, propenyl, and propyl compounds in the rat. Toxicol. Appl. Pharmacol. 6 (4), 378–387.
Thompson, D., Constantin-Teodosiu, D., Egestad, B., Mickos, H., Moldeus, P., 1990. Formation of glutathione conjugates during oxidation of eugenol by microsomal fractions of rat liver and lung. Biochem. Pharmacol. 39 (10), 1587–1595.
Thompson, D., Constantin-Teodosiu, D., Norbeck, K., Svensson, B., Moldeus, P., 1989. Metabolic activation of eugenol by myeloperoxidase and polymorphonuclear leukocytes. Chem. Res. Toxicol. 2 (3), 186–192.
Thompson, D.C., Constantin-Teodosiu, D., Moldeus, P., 1991. Metabolism and cytotoxicity of eugenol in isolated rat hepatocytes. Chem. Biol. Interact. 77, 137–147.
Thompson, D.G., Barhoumi, R., Burghardt, R.C., 1998. Comparative toxicity of eugenol and its quinone methide metabolite in cultured liver cells using kinetic fluorescence bioassays. Toxicol. Appl. Pharmacol. 149 (1), 55–63.
Tsutsui, T., Suzuki, N., Kobayashi, Y., Suzuki, H., Fukuda, S., Maizumi, H., 1987. Assessment of the carcinogenic hazard of 27 substances used in dental practices. Jpn. J. Pharmacol. 43, 132P.
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, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
Van Duuren, B.L., Goldschmidt, B.M., 1976. Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. J. Natl. Cancer Inst. 56 (6), 1237–1242.
Van Duuren, B.L., Sivak, A., Segal, A., Orris, L., Langseth, L., 1966. The tumor promoting agents of tobacco leaf and tobacco smoke condensate. J. Natl. Cancer Inst. 37 (4), 519–526.
Vishteh, A., Thomas, I., Imamura, T., 1986. Eugenol modulation of the immune response in mice. Immunopharmacology 12, 187–192.
Ward, J.M., Tsuda, H., Tatematsu, M., Hagiwara, A., Ito, N., 1989. Hepatotoxicity of agents that enhance formation of focal hepatocellular proliferative lesions (putative preneoplastic foci) in a rapid rat liver bioassay. Fund. Appl. Toxicol. 12 (1), 163–171.
Weinberg, J.E., Rabinowitz, J.L., Zanger, M., Gennaro, A.R., 1972. C-14-Eugenol: I. synthesis, polymerization, and use. J. Dent. Res. 51 (45), 1055–1061.
Zhao, K., Singh, J., 1998. Mechanisms of percutaneous absorption of tamoxifen by terpenes: eugenol, d-limonene and menthone. J. Contr. Release 55, 253–260.