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Short review

RIFM fragrance ingredient safety assessment, Eugenol, CAS Registry Number 97-53-0

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ABSTRACT

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Reproductive toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 230 mg/kg/day. A gavage multigenerational continuous breeding study conducted in rats on a suitable read across analog resulted in a MOE of 12,105 while considering 22.6% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

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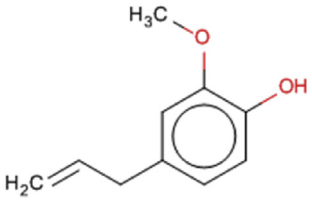


Abbreviation list:
2-Box model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th **percentile**- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al., 2002 and Ford et al., 2000.
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; Safford et al., 2015) 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
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
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel[a] concludes that this material is safe under the limits described in this safety assessment.

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

Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

Summary: The use of this material under current use conditions is supported by the existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Reproductive toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 230 mg/kg/day. A gavage multigenerational continuous breeding study conducted in rats on a suitable read across analog resulted in a MOE of 12,105 while considering 22.6% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

Human health safety assessment	
Genotoxicity: Not genotoxic	(Pool and Lin, 1982; Sekizawa and Shibamoto, 1982; Shelby et al., 1993)
Repeated dose toxicity: NOAEL = 300 mg/kg/day	(NTP, 1983)
Developmental and reproductive toxicity: NOAEL = 230 mg/kg/day	(NTP, 2002)
Skin sensitization: NESIL = 5900 μg/cm^2	(RIFM, 2001)
Phototoxicity/photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM DB; RIFM, 1981)
Local respiratory toxicity: NOAEC = 100 mg/m^3 (0.1 mg/L)	(RIFM, 2012)
Environmental safety assessment	
Hazard assessment:	
Persistence: Critical Measured Value: 100.4% (OECD 301B)	(RIFM, 1994a)
Bioaccumulation: Screening Level: 14.6 L/Kg	(EPISUITE ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48 h *Daphnia magna* EC50: 1.13 mg/l	(REACH dossier, 2013)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical ecotoxicity endpoint: 48 h *Daphnia magna* EC50: 1.13 mg/l	
RIFM PNEC is: 1.13 μg/l	
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe <1	

[a] RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

1. Identification

1 **Chemical Name:** Eugenol
2 **CAS Registry Number:** 97-53-0
3 **Synonyms:** 4-Allylcatechol-2-methyl ether, 4-Allylguaiacol, 4-Allyl-2-methoxyphenol, Eugenol, 1-Hydroxy-2-methoxy-4-propenylbenzene, 4-Hydroxy-3-methoxy-1-allylbenzene, 2-Methoxy-4-allylphenol, Phenol, 2-methoxy-4-(2-propenyl)-, 1-Allyl-4-hydroxy-3-methoxybenzene, Eugenic acid, Caryophyllic acid, Allylguaiacol, 2-Methoxy-4-(2-propenyl)phenol, 1-Hydroxy-2-methoxy-4-allylbenzene, 2-Hydroxy-5-allylanisole, o-ﾒﾄｷｼ-p-ﾌﾟﾛﾍﾟﾆﾙﾌｪﾉｰﾙ, Eugenol pure cosmos
4 **Molecular Formula:** $C_{10}H_{12}O_2$
5 **Molecular Weight:** 164.2
6 **RIFM Number:** 123

2. Physical data

1 **Boiling Point:** 255 °C [FMA], (calculated) 264.26 °C [EPI Suite]
2 **Flash Point:** >212 °F; CC [FMA]
3 **Log K_{OW}:** 2.0 [RIFM, 2010a], 2.99 [Abraham and Rafols, 1995], 2.4 [RIFM, 1996], 2.0 at 24 °C [RIFM, 1994b], 2.73 [EPI Suite]
4 **Melting Point**: 60.57 °C [EPI Suite]
5 **Water Solubility:** 754 mg/L [EPI Suite]
6 **Specific Gravity:** 1.07 g/ml [RIFM, 1994c], 1.066–1.072 [FMA], 1.064–1.070 [FMA]
7 **Vapor Pressure:** 0.00574 mm Hg @ 20 °C [EPI Suite 4.0], 0.009 mm Hg 20 °C [FMA], 0.00948 mm Hg @ 25 °C [EPI Suite]
8 **UV Spectra**: Minor absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} cm^{-1})
9 **Appearance/Organoleptic**: A colorless or very pale straw-colored, oily liquid. Powerful, warm-spicy, rather dry and almost sharp odor, drier and harder than that of clove bud oil, less peppery-woody than that of clover leaf oil. Warm-spicy taste, somewhat burning unless highly diluted (Arctander, 1969).

3. Exposure

1 **Volume of Use (worldwide band):** 100–1000 metric tons per year	(IFRA, 2011)
2 **Inhalation Exposure[a]:** 0.0005 mg/kg/day	(RIFM, 2013)
3 **Total Systemic Exposure (Dermal, Oral and Inhalation)[b]:** 0.0018 mg/kg/day	(RIFM, 2013)

[a] 95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015, Safford et al., 2015).

[b] 95th percentile calculated exposure; assumes 100% dermal absorption, derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015).

4. Derivation of systemic absorption

1 **Dermal:** 22.6%

Liu and Hotchkiss, 1997a,b: An *in vitro* skin absorption study was conducted using human skin with radiolabelled eugenol 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%.

2 **Oral:** Data considered in Creme model.
3 **Inhalation:** Assumed 100%
4 **Total:** Dermal (22.6%) + Inhalation (100%) absorbed = 0.0018 mg/kg/day

5. Computational toxicology evaluation

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

Expert judgment	Toxtree 2.6	OECD QSAR Toolbox 3.2
I	I	I

d **Skin Sensitization**: None
e **Phototoxicity/Photoallergenicity**: None
f **Local Respiratory Toxicity**: Isoeugenol (CAS # 97-54-1)
g **Environmental Toxicity**: None
3 **Read across justification**: See Appendix below

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

Eugenol is reported to occur in the following foods[1] and in some natural complex substances (NCS):

Acerola (Malpighia)	Ashanti pepper (Piper guineense Schum and Thom)
Agastache species	Banana (Musa sapientum L.)
Anise (Pimpinella anisum L.)	BeerBeli, bael (Aegle marmelos Correa)
Anise brandy	Black choke berry (Aronia melanocarpa Ell.)
Apple brandy (Calvados)	Black currants (Ribes nigrum L.)
Apple fresh (Malus species)	Buchu oil
Apricot (Prunus armeniaca L.)	Buckwheat
Arctic bramble (Rubus arcticus L.)	Grape brandy
Artichoke	Guava and feyoa
Calamus (sweet flag) (Acorus calamus L.)	Guava wine
Capsicum species	Honey
Carrot (Daucus carota L.)	Katsuobushi (dried bonito)
Celery (Apium graveolens L.)	Kumazasa (Sasa albo-marginata)
Cherry	Lamb's lettuce (Valerianella locusta)
Chervil (Anthriscus cerefolium L.)	Laurel (Laurus nobilis L.)
Chinese quince (Pseudocydonia sinensis Schneid)	Lemon balm (Melissa officinalis L.)
Cider (apple wine)	Licorice (Glycyrrhiza glabra L.)
Cinnamomum species	Macadamia nut (Macadamia integrifolia)
Citrus fruits	Mace (Myristica fragrans Houttuyn)
Cloudberry (Rubus chamaemorus L.)	Mangifera species
Cloves (Eugenia caryophyllata Thunberg)	Mastic (Pistacia lentiscus)
Cocoa category	Mate (Ilex paraguayensis)
Coffee	Melon
Crispbread	Mentha oils
Cuttlefish	Mushroom
Date (Phoenix dactylifera L.)	Myrtle (Myrtus communis L.)
Dill (Anethum species)	Nutmeg (Myristica fragrans Houttuyn)
Elderberry (Sambucus nigra L.)	Ocimum species
Fenugreek (Trigonella foenum-graecum L.)	Okra (Hibiscus esculentus L.)
Fig (Ficus carica L.)	Origanum (Spanish) (Coridothymus cap.(L.) Rchb.)
Fish	Sherry
Ginger (Zingiber species)	Strawberry (Fragaria species)
Passion fruit (Passiflora species)	Sweet grass oil (Hierochloe odorata)
Pepper (Piper nigrum L.)	Sweet marjoram (Origanum majorana L.)
Pimento (allspice) (Pimenta dioica L. Merr.)	Syzygium species
Piper betle L. cultivars	Tamarind (Tamarindus indica L.)
Plum (Prunus species)	Tapereba, caja fruit (Spondias lutea L.)
Plum brandy	Tarragon (Artemisia dracunculus L.)
Plum wine	Tequila (Agave tequilana)
Pork	Thyme (Thymus species)
Quince, marmelo (Cydonia oblonga Mill.)	Tomato (Lycopersicon esculentum Mill.)
Raspberry, blackberry and boysenberry	Vaccinium species
Rhubarb	Vanilla
Rooibos tea (Aspalathus linearis)	Whisky
Rosemary (Rosmarinus officinalis L.)	Wine
Rum	Wormwood oil (Artemisia absinthium L.)
Salvia species	
Satureja species	
Sea buckthorn (Hippophaë rhamnoides L.)	

2 **Analogues Selected:**
a **Genotoxicity**: None
b **Repeated Dose Toxicity**: None
c **Developmental and Reproductive Toxicity**: Isoeugenol (CAS # 97-54-1)

[1] 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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

7. IFRA standard

None.

8. REACH dossier

Available; accessed on 9/12/2013.

9. Summary

9.1. Human health endpoint summaries

9.1.1. Genotoxicity

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

9.1.1.1. Risk assessment. The mutagenic potential of eugenol was tested in an Ames assay conducted equivalent to OECD TG 471 using the standard plate incorporation method (Pool and Lin, 1982; Sekizawa and Shibamoto, 1982). *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 were tested with eugenol in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate and eugenol was considered not mutagenic.

The clastogenic potential of eugenol was assessed in an *in vivo* micronucleus assay headed by the National Toxicology Program (NTP) and conducted equivalent to OECD TG 464 with minor deviation. No genotoxic activity was observed, as the percentage of micronucleated PCEs in all treated animals was less than that of the controls (Shelby et al., 1993).

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

Additional references: NTP, 1983; Swanson, 1979; To, 1982; Rockwell, 1979; Florin, 1980; Ishidate, 1984; Nestmann, 1980; Hayashi, 1984; Stich, 1981a; Nestmann, 1983; Phillips, 1984; Eder, 1980; Eder1982a; Randerath, 1984; Rapson, 1980; Yoshimura, 1981; Stich, 1981b; Green, 1978; Dorange, 1976; Haworth, 1983; Eder, 1982b; Douglas, 1980; Amonkar, 1986; Jansson, 1986; Jansson, 1985; Ishidate, 1982; Fukuda, 1987; Woolverton, 1986a; Tsutsui, 1987; Hayashi, 1988; Galloway, 1987; Ohshima, 1989; Miller, 1986; Orstavik, 1985; Schunk, 1988; Maura, 1989; Schiestl, 1989; Howes, 1990a; Phillips, 1990; Sasaki, 1989; Armstrong, 1992; Tennant, 1987; Elmore, 1989; Allavena, 1992; Howes, 1990b; Bean, 1992; Bean, 1993; Schiestl, 1993; Ellahuene, 1994; Myhr, 1991; Azizan, 1995; Rompelberg et al., 1995a, 1996a, 1996b; Sukumaran, 1995; Storer, 1996; Rompelberg, 1996c; Burkey, 1998; Bodell, 1998; Rompelberg et al., 1995b, 1995c, 1995d, 1995e; Mulky, 1987; Lewis-Burkey, 2000; Abraham, 2001; Fahim, 2001; RIFM, 1980; Yasunaga, 2004; Oda, 1978; Foureman, 1994; Iida, 2007; Hikiba, 2005; Maralhas, 2006; Woolverton, 1986b; Someya, 2008; Kono, 1995; Martins, 2011; Hughes, 2012; Reus, 2012; Fowler, 2012

Literature Search and Risk Assessment Completed on: 09/16/13.

9.1.2. Repeated dose toxicity

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

9.1.2.1. Risk assessment. The NOAEL for repeated dose toxicity of eugenol 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).

RIFM's Expert Panel[2] 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 to the development of liver tumors by non-genotoxic mechanisms. The total systemic exposure to eugenol is 0.019 mg/kg/day, which is more than 23,600 times lower than the lowest dose level in the mouse NTP study. **Therefore, the MOE is equal to the NOAEL for eugenol in mg/kg/day divided by the total systemic exposure, 300/0.019 or 15789.**

Additional references: 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; 1967; Rompelberg et al., 1995b; Ward et al., 1989; RIFM, 1958; RIFM, 1954; Bar and Griepentrog, 1967; Van Duuren et al., 1966, VanDuuren and Goldschmidt, 1976; 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; Miller; 2001; Fischer et al., 1990; Sutton, 1986; Caldwell et al., 1985; Delaforge et al., 1980, 1976; Weinberg et al., 1972; Green and Tephly, 1996; Thompson et al., 1989; Meredith et al., 2009; Boutin et al., 1981; 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 et al., 1990; Laekeman et al., 1990; Schroder and Vollmer, 1932; Thompson et al., 1998; Meyer and Meyer, 1959; Meyer, 1965; Jimbo, 1983; Liu and Hotchkiss, 1996; Liu and Hotchkiss, 1997a,b; RIFM, 1996; Hotchkiss, 1998; Zhao and Singh, 1998; Schmitt et al., 2009, 2010; Clegg, 1965; Hansen and Meyer, 1978, Hansen et al., 1982; Wurtzen and Olsen, 1986; Telford et al., 1962; Vorhees et al., 1981; Allen, 1976; Jeong et al., 2005; Kavlock, 1990; RIFM, 2010b; RIFM, 2012; Singal et al., 2013; Fang et al., 2003, 2001; Nishihara et al., 2000; Badger et al., 1999; Badger et al., 2002; Liu and Hotchkiss, 1998; Petridou-Fischer et al., 1987; Fuciarelli et al., 2000; 2001; Seto and Keup, 1969; Jimbo et al., 1983; Liu and Hotchkiss, 1996; Liu and Hotchkiss, 1997a,b; Madsen et al., 2011.

Literature Search and Risk Assessment Completed on: 09/16/13.

9.1.3. Developmental and reproductive toxicity

The margin of exposure for eugenol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

9.1.3.1. Risk assessment. The developmental toxicity data on eugenol are insufficient. Read across material isoeugenol (CAS # 97-54-1; see Section V) has a gavage developmental toxicity study conducted in rats which determined the NOAEL for developmental toxicity to be 500 mg/kg/day, based on intrauterine growth retardation and delayed skeletal ossification. These effects occurred at maternally toxic dosages (George et al., 2001; NTP, 1999). **Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.019 or 26316.**

There are no reproductive toxicity data on eugenol. Read across material isoeugenol (CAS # 97-54-1) has a gavage multigenerational continuous breeding study conducted in rats which determined the NOAEL for reproductive toxicity to be 230 mg/kg/day, based on a decreased number of male pups per litter during the F0 cohabitation and decreased male and female pup weights during

[2] RIFM's Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Table 1
Eugenol – data summary.

LLNA weighted mean EC3 value [No. Studies]	Potency classification based on animal data[a]	Human data			
		NOEL-HRIPT (induction) μg/cm[b]	NOEL-HMT (induction) μg/cm[b]	LOEL[b] (induction) μg/cm[b]	WoE NESIL[c]
2703 [6]	Weak	5906	NA	NA	5900

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.

the F1 cohabitation (NTP, 2002; Layton et al., 2001). **Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 230/0.019 or 12105.**

Additional references: 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; 1967; Rompelberg et al., 1995b; Ward et al., 1989; RIFM, 1958; RIFM, 1954; Bar and Griepentrog, 1967; Van Duuren et al., 1966, VanDuuren and Goldschmidt, 1976; 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; Miller; 2001; Fischer et al., 1990; Sutton, 1986; Caldwell et al., 1985; Delaforge et al., 1980, 1976; Weinberg et al., 1972; Green and Tephly, 1996; Thompson et al., 1989; Meredith et al., 2009; Boutin et al., 1981, 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 et al., 1990; Laekeman et al., 1990; Schroder and Vollmer, 1932; Thompson et al., 1998; Meyer and Meyer, 1959; Meyer, 1965; Jimbo, 1983; Liu and Hotchkiss, 1996, Liu and Hotchkiss, 1997a,b; RIFM, 1996; Hotchkiss, 1998; Zhao and Singh, 1998; Schmitt et al., 2009, 2010; Clegg, 1965; Hansen and Meyer, 1978, Hansen et al., 1982; Wurtzen and Olsen, 1986; Telford et al., 1962; Vorhees et al., 1981; Allen, 1976; Jeong et al., 2005; Kavlock, 1990; RIFM, 2010b; RIFM, 2012; Singal et al., 2013; Fang et al., 2003, 2001; Nishihara et al., 2000; Badger et al., 1999; Badger et al., 2002; Liu and Hotchkiss, 1998; Petridou-Fischer et al., 1987; Fuciarelli et al., 2000; 2001; Seto and Keup, 1969; Jimbo et al., 1983; Liu and Hotchkiss, 1996; Liu and Hotchkiss, 1997a,b; Madsen et al., 2011.

Literature Search and Risk Assessment Completed on: 09/16/13.

9.1.4. Skin Sensitization

Based on the existing data, summarized in the existing IFRA Standard, eugenol is considered to be a weak skin sensitizer with a defined NESIL of 5900 μg/cm^2.

9.1.4.1. Risk assessment. The available data demonstrate that eugenol is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 5900 μg/cm^2 (Table 1) (Gerberick et al., 2009; RIFM, 2001). Utilizing the available NESIL, the application of the Quantitative Risk Assessment (QRA) described by Api and Vey (2008) results in the acceptable exposure limits summarized in Table 2.

Additional references: None.

Literature Search and Risk Assessment Completed on: 09/16/13.

9.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and existing data, eugenol would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 2
Eugenol – Acceptable exposure limits.

QRA Category[a]	Examples of product type	Calculated QRA
1	Lip Products	0.17%
2	Deodorant/Antiperspirant	0.22%
3	Hydroalc., Shaved Skin	0.89%
4	Hydroalc., Unshaved Skin	2.67%
5	Women Facial Cream	1.40%
6	Mouthwash	4.28%
7	Intimate Wipes	0.45%
8	Hair Styling Aids Non-Spray	5.96%
9	Conditioners, Rinse-off	29.50%
10	Hard Surface Cleaners	49.17%
11	Candle (Non-Skin/Incidental Skin)	Not restricted

[a] Note: For a description of the categories, refer to the QRA Informational Booklet. (www.rifm.org/doc/QRAInfoJuly201.pdf).

9.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark, 1000 L mol^{-1} · cm^{-1}, of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In a rat phototoxicity study, topical application of a 30% solution of eugenol followed by UV exposure did not result in phototoxic reactions (RIFM, 1981). Based on lack of significant absorbance in the critical range and *in vivo* study data, Eugenol does not present a concern for phototoxicity or photoallergenicity.

Additional references: None.

Literature Search and Risk Assessment Completed on: 08/26/15.

9.1.6. Local respiratory toxicity

The margin of exposure for eugenol is adequate for the respiratory endpoint at the current level of use.

9.1.6.1. Risk assessment. An inhalation study on read across material, isoeugenol, was evaluated by the Respiratory Core Team[3] (RIFM, 2012). Neither a no-observed-adverse-effect concentration (NOAEC), nor a no-observed-effect concentration (NOEC) could be determined for this study regarding upper airway irritation. For the lower airway, the NOEC was considered to be 100 mg/m^3 (0.1 mg/L).

Additional references: Beroza, 1975; Clark, 1988; RIFM, 1977; RIFM, 1997; Miyazaki, 1992; Buchbauer, 1993; Regnault-Roger, 1995; Perrucci, 1995; Robin, 1998; Isola, 2003; RIFM, 2003a; Rogers, 2003; Leclerc et al., 2002; RIFM, 2003b; Isola, 2003a; Isola, 2004; Smith, 2004; RIFM, 2004; Isola, 2004b; Rogers, 2005; Vethanayagam, 2013.

Literature Search and Risk Assessment Completed on: 09/16/13.

9.2. Environmental endpoint summary

9.2.1. Screening-level assessment

A screening level risk assessment of eugenol was performed

[3] Respiratory Core Team is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Following the RIFM Environmental Framework, eugenol 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 EPISUITE ver 4.1 did identify eugenol as being possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical–chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

9.2.2. Risk assessment

Based on current VoU (2011), eugenol presents a risk to the aquatic compartment.

9.2.3. Key studies

9.2.3.1. Biodegradation. RIFM, 1997: Biodegradation of the test material was evaluated by a modified MITI test according to OECD Guideline 301C. A closed flask containing mineral medium inoculated with activated sludge and 100 mg/l of eugenol was incubated for 28 days. The biodegradation rate was 79% after 7 days and 97% after 28 days.

RIFM, 1994: Biodegradation was evaluated by the sealed vessel test based on OECD Guideline 301B. 10 mg/l of eugenol was incubated for 28 days. The biodegradation rate was 65.7% at day 10 and 100.4% at day 28.

RIFM, 1999: The biodegradability of the test material was determined using the Closed Bottle Test according to 92/69/EEC, Method C.4-E method. Within the test period of 28 days, a degradation of 82% was observed.

9.2.3.2. Ecotoxicity. RIFM, 1999: A 48 h *Daphnia magna* acute toxicity study was conducted according to the 92/69/EEC C.1 method. The geometric mean of EC0/EC100 was 1.05 mg/l.

9.2.4. Other available data

Eugenol has been registered under REACH and additional data is available (accessed 09/30/2013): A 96 h fish (*Danio rerio*) acute study according to OECD 203 method was conducted and the LC50 was reported to be 13 mg/l. *D. magna* acute toxicity test according to the OECD 202 method was conducted, and the 48 h EC50 was reported to be 1.13 mg/l 72 h algae inhibition test according to the OECD 201 method was conducted. The EC50 was 23 mg/l, 36 mg/l and 24 mg/l based on cell number, biomass and growth rate, respectively.

9.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	221.5 mg/l			1,000,000	0.2215 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	7.938 mg/l	3.309 mg/l	14.17 mg/l	10,000	0.3309 μg/l	Phenols
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	29.76 mg/l	18.07 mg/l	17.80 mg/l			Neutral Organics
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	13 mg/l					
Daphnia		1.13 mg/l		1000	1.13 μg/l	
Algae		23 mg/l				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.0	2.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 1.13 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use**.**

Literature Search and Risk Assessment Completed on: 09/16/13.

10. Literature search[4]

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2015.12.013.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.12.013.

Appendix

Summary

There are insufficient toxicity data on Eugenol (RIFM # 123, CAS # 97-53-0). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

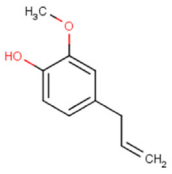
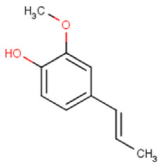
Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analog were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/rationale

- Isoeugenol (analog) was used as a read-across for eugenol (target) based on:
  - The target and analog both belong to the generic class of phenols. Both are p-alkyl phenols.
  - They are structural isomers with common structures of *o*-methoxy-phenol and an alkene chain.
  - The only difference is in the position of the double bond in alkene chain, which is terminal in target and internal in analog. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - The target and analog show similar alerts for ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - The target and analog show similar alerts for protein binding.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

[4] Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

	Target Material	Read across Material
Principal Name	Eugenol	Isoeugenol
CAS No.	97-53-0	97-54-1
Structure		
3D Structure	http://www.thegoodscentscompany.com/opl/97-53-0.html	http://www.thegoodscentscompany.com/opl/97-54-1.html
Read-across endpoint		• Devel/Repro • Respiratory
Molecular Formula	C10H12O2	C10H12O2
Molecular Weight	164.21	164.21
Melting Point (°C, EPISUITE)	60.57	61.93
Boiling Point (°C, EPISUITE)	264.26	270.60
Vapor Pressure (Pa @ 25°C, EPISUITE)	1.264	0.508
Log Kow (KOWWIN v1.68 in EPISUITE)	2.73	2.65
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	754	165.9
J_{max} (mg/cm^2/h, SAM)	150.1217708	48.47103916
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	0.00487	0.002701
Similarity (Tanimoto score)[1]		64%
In silico Results for Target and Analog		
Developmental and Reproductive Toxicity		
ER binding (OECD)	Weak binder, OH group	Weak binder, OH group
Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (low reliability)	NON-Toxicant (low reliability)
Metabolism		
Rat liver S9 metabolism simulator (OECD)	See Supplemental data 1	See Supplemental data 2

[1] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).

References

Abraham, M.H., Rafols, C., 1995. Factors that influence tadpole narcosis. An LFER analysis. J. Chem. Soc. – Perkin Trans. 2 (10), 1843–1851.

Abraham, S.K., 2001. Anti-genotoxicity of trans-anethole and eugenol in mice. Food Chem. Toxicol. 39 (5), 493–498.

Allavena, A., Martelli, A., Robbiano, L., Brambilla, G., 1992. Evaluation in a battery of in vivo assays of four in vitro genotoxins proved to be noncarcinogens in rodents. Teratog. Carcinog. Mutagen. 12 (1), 31–41.

Allen, J.R., 1976. Long-term antioxidant exposure effects on female primates. Arch. Environ. Health 31, 47–50.

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.

Amonkar, A.J., Nagabhushan, M., D'souza, A.V., Bhide, S.V., 1986. Hydroxychavicol: a new phenolic antimutagen from betel leaf. Food Chem. Toxicol. 24 (12), 1321–1324.

Api, A.M., Vey, M., 2008. Implementation of the dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. Regul. Toxicol. Pharmacol. 52 (1), 53–61.

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., Renkers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Arctander, S., 1969. Perfume and Flavor Chemicals, Vols. I and II. Author, Montclair, NJ (USA).

Armstrong, M.J., Bean, C.L., Galloway, S.M., 1992. A quantitative assessment of the cytotoxicity associated with chromosomal aberration detection in Chinese hamster ovary cells. Mutat. Res. Fundam. Mol. Mech. Mutagen. 265 (1), 45–60.

Azizan, A., Blevins, R.D., 1995. Mutagenicity and antimutagenicity testing of six chemicals associated with the pungent properties of specific spices as revealed by the Ames Salmonella/microsomal assay. Arch. Environ. Contam. Toxicol. 28 (2), 248–258.

Badger, D.A., Kattnig, M.J., Smith, R.L., Bao, J., Sipes, I.G., 1999. The disposition of isoeugenol in the male Fischer-344 rat. Toxicol. 48 (1-S), 224.

Badger, D.A., Smith, R.L., Bao, J., Kuester, R.K., Sipes, I.G., 2002. Disposition and metabolism of isoeugenol in the male Fischer 344 rat. Food Chem. Toxicol. 40 (12), 1757–1765.

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). Med. Ernahr. 8, 244–251.

Bean, C.L., Armstrong, M.J., Galloway, S.M., 1992. Effect of sampling time on chromosome aberration yield for 7 chemicals in Chinese hamster ovary cells. Mutat. Res. Fundam. Mol. Mech. Mutagen. 265 (1), 31–44.

Bean, C.L., Galloway, S.M., 1993. Evaluation of the need for a late harvest time in the assay for chromosome aberrations in Chinese hamster ovary cells. Mutat. Res. Environ. Mutagen. Relat. Subj. 292 (1), 3–16.

Beroza, M., Inscoe, M.N., Schwartz, P.H., Keplinger, M.L., Mastri, C.W., 1975. Acute toxicity studies with insect attractants. Toxicol. Appl. Pharmacol. 31 (3), 421–429.

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. Former. Fundam. Appl. Toxicol. 54 (1), 138–153.

Bodell, W.J., Ye, Q., Pathak, D.N., Pongracz, K., 1998. Oxidation of eugenol to form DNA adducts and 8-hydroxy-2'-deoxyguanosine: role of quinone methide derivative in DNA adduct formation. Carcinogenesis 19 (3), 437–443.

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. 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. Proc. Soc. Exp. Biol. Med. 80, 144–146.

Buchbauer, G., Jirovetz, L., Jáger, W., Plank, C., Dietrich, H., 1993. Fragrance compounds and essential oils with sedative effects upon inhalation. J. Pharm. Sci. 82 (6), 660–664.

Burkey, J.L., Sauer, J.M., McQueen, C.A., Sipes, I.G., 1998. The cytotoxicity and genotoxicity of safrole and related congeners. Toxicol. 42 (1-S), 78.

Cadby, P.A., Troy, W.R., Vey, M.G.H., 2002. Consumer exposure to fragrance ingredients: providing estimates for safety evaluation. Regul. Toxicol. Pharmacol. 36 (3), 246–252.

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.

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.

Clark, G.C., 1988. Acute inhalation toxicity of eugenol in rats. Arch. Toxicol. 62 (5), 381–386.

Clegg, D.J., 1965. Absence of teratogenic effect of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) in rats and mice. Food Cosmet. Toxicol. 3, 387–403.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., Mahony, C.O., 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.

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. Mass Spec. Biochem. Med. 2, 65–89.

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.

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.

Douglas, G.R., Nestmann, E.R., Betts, J.L., Mueller, J.C., Lee, E.G.H., Stich, H.F., Walden, C.C., 1980. Mutagenic activity in pulp mill effluents. Water Chlorination Environ. Impact Health Eff. 3, 865–880.

Dorange, J.L., Delaforge, M., Janiaud, P., Padieu, P., 1976. Mutagenicity of the metabolites of the epoxide-diol pathway of safrole and its analogs. Study on *Salmonella typhimurium*. C. R. Seances Soc. Biol. Ses Fil. 171 (5), 1041–1048.

Eder, E., Neudecker, T., Lutz, D., Henschler, D., 1980. Mutagenic potential of allyl and allylic compounds: structure-activity relationship as determined by alkylating and direct in vitro mutagenic properties. Biochem. Pharmacol. 29 (7), 993–998.

Eder, E., Neudecker, T., Lutz, D., Henschler, D., 1982a. Correlation of alkylating and mutagenic activities of allyl and allylic compounds: standard alkylation test vs. kinetic investigation. Chem. Biol. Interact. 38 (3), 303–315.

Eder, E., Henschler, D., Neudecker, T., 1982b. Mutagenic properties of allylic and α, β-unsaturated compounds: consideration of alkylating mechanisms. Xenobiotica 12 (12), 831–848.

Ellahueñe, M.F., Pérez-Alzola, L.P., Orellana-Valdebenito, M., Muñoz, C., Lafuente-Indo, N., 1994. Genotoxic evaluation of eugenol using the bone marrow micronucleus assay. Mutat. Res. Genet. Toxicol. 320 (3), 175–180.

Elmore, E., Fitzgerald, M.P., 1989. Evaluation of the bioluminescence assays as screens for genotoxic chemicals. Prog. Clin. Biol. Res. 340, 379–387.

Essential Estimation Programs Interface (EPI) SuiteTM (version 4.1) [Software]. (Copyright 2000-2011). US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Retrieved from http://www.epa.gov/opptintr/exposure/pubs/episuite.htm Research, 20(6), 482–487.

Fahim, F.A., Chipman, J.K., 2001. Illustration of the antioxidant and/or antimutagenic effect of eugenol on HepG2 cells treated with AF-B1 using single cell gel electrophoresis (Comet assay) and electron microscopy (EM). Cancer Mol. Biol. 8, 1599–1612.

Fang, H., Tong, W., Shi, L.M., Blair, R., Perkins, R., Branham, W., Hass, B.S., Xie, Q., Dial, S.L., Moland, C.L., Sheehan, D.M., 2001. Structure-activity relationships for a large diverse set of natural, synthetic, and environmental estrogens. Chem. Res. Toxicol. 14 (3), 280–294.

Fang, H., Tong, W., Branham, W.S., Moland, C.L., Dial, S.L., Hong, H., Xie, Q., Perkins, R., Owens, W., Sheehan, D.M., 2003. Study of 202 natural, synthetic, and environmental chemicals for binding to the androgen receptor. Chem. Res. Toxicol. 16, 1338–1358.

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 tabacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15 (3), 219–232.

Ford, R.A., Domeyer, B., Easterday, O., Maier, K., Middleton, J., 2000. Criteria for development of a database for safety evaluation of fragrance ingredients. Regul. Toxicol. Pharmacol. 31 (2), 166–181.

Foureman, P., Mason, J.M., Valencia, R., Zimmering, S., 1994. Chemical mutagenesis testing in Drosophila. IX. Results of 50 coded compounds tested for the National Toxicology Program. Environ. Mol. Mutagen. 23 (1), 51–63.

Fowler, P., Smith, K., Young, J., Jeffrey, L., Kirkland, D., Pfuhler, S., Carmichael, P., 2012. Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell type. Mutat. Res. Genet. Toxicol. Environ. Mutagen. 742 (1), 11–25.

Fuciarelli, A.F., Moore, R.J., Phelps, R.L., Pierce, J.T., Baum, S.R., Dill, J.A., Johnson, J.D., Graves, S.W., Smith, C.S., 2000. Preliminary toxicokinetic studies of isoeugenol (IEG) in female fischer 344/N rats and B6C3F1 mice. Toxicol. 54 (1), 54.

Fuciarelli, A.F., Moore, R.J., Lee, K.M., Pierce, J.T., Bates, J.D., Dill, J.A., Johnson, J.D., Graves, S.W., Godfrey, V.B., Smith, C.S., 2001. Single-administration toxicokinetic

studies of isoeugenol (IEG) in Fischer 344/N rats and B6C3F1 mice. Toxicol. 60 (1), 341.
Fukuda, S., 1987. Assessment of the carcinogenic hazard of 6 substances used in dental practices. (1) Morphological transformation, DNA damage and sister chromatid exchanges in cultured Syrian hamster embryo cells induced by carbol camphor, eugenol, thymol, EDTA, benzalkonium chloride and benzethonium chloride. Shigaku = Odontol. J. Nihon Dent. Coll. 74 (6), 1365.
Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Rimpo, J., 1987. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ. Mol. Mutagen. 10 (S10), 1–35.
Gardner, I., Bergin, P., Stening, P., Kenna, J.G., Caldwell, J., 1995. Protein adducts derived from methyleugenol. ISSX Int. Meet. 4th (8), 208.
George, J.D., Price, C.J., Marr, M.C., Myers, C.B., Jahnke, G.D., 2001. Evaluation of the developmental toxicity of isoeugenol in Sprague-Dawley (CD) rats. Toxicol. Sci. Former. Fundam. Appl. Toxicol. 60 (1), 112–120.
Gerberick, G.F., Troutman, J.A., Foertsch, L.M., Vassallo, J.D., Quijano, M., et al., 2009. Investigation of peptide reactivity of pro-hapten skin sensitizers using a peroxidase-peroxide oxidation system. Toxicol. Sci. 112 (1), 164–174.
Golberg, L., 1978. Cell metabolism of safrole, isosafrole and eugenol. Food Chem. Toxicol. 16, 294.
Green, N.R., Savage, J.R., 1978. Screening of safrole, eugenol, their ninhydrin positive metabolites and selected secondary amines for potential mutagenicity. Mutat. Res. Fundam. Mol. Mech. Mutagen. 57 (2), 115–121.
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., 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.
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 Cosmet. Toxicol. 5 (2), 141–157.
Hansen, E., Meyer, O., 1978. A study of the teratogenicity of butylated hydroxyanisole on rabbits. Toxicology 1092), 195–201.
Hansen, E., Meyer, O., Olsen, P., 1982. Study on toxicity of butylated hydroxyanisole (BHA) in pregnant gilts and their foetuses. Toxicology 23 (1), 79–83.
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.
Hayashi, M., Sofuni, T., Ishidate, M., 1984. A pilot experiment for the micronucleus test: the multi-sampling at multi-dose levels method. Mutat. Res. Lett. 141 (3), 165–169.
Hayashi, M., Kishi, M., Sofuni, T., Ishidate, M., 1988. Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. Food Chem. Toxicol. 26 (6), 487–500.
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
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. Cancer 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. Fragr Benef. Advers. Eff. 125–135.
Howes, A.J., Chan, V.S.W., Caldwell, J., 1990a. Structure-specificity of the genotoxicity of some naturally occurring alkenylbenzenes determined by the unscheduled DNA synthesis assay in rat hepatocytes. Food Chem. Toxicol. 28 (8), 537–542.
Howes, A.J., Chan, V.S.W., Caldwell, J., 1990b January. Induction of unscheduled DNA-synthesis in cultured rat Hepatocytes by natural food flavors. Mutagenesis 5 (1), pp. 85–85, Walton St Journals Dept, Oxford, England OX2 6DP: Oxford Univ. Press United Kingdom.
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.
Hughes, C., Rabinowitz, A., Tate, M., Birrell, L., Allsup, J., Billinton, N., Walmsley, R.M., 2012. Development of a high-throughput *Gaussia* luciferase reporter assay for the activation of the GADD45a gene by mutagens, promutagens, clastogens, and aneugens. J. Biomol. Screen. 1087057112453312.
IFRA (International Fragrance Association), 2011. Volume of Use Survey, February 2011.
Iida, M., Anna, C.H., Gaskin, N.D., Walker, N.J., Devereux, T.R., 2007. The putative tumor suppressor Tsc-22 is downregulated early in chemically induced hepatocarcinogenesis and may be a suppressor of Gadd45b. Toxicol. Sci. 99 (1), 43–50.
Ishidate Jr., M., 1982. Mammalian cell systems as a screening tool for the detection of possible mutagens and/or carcinogens in the environment. J. Hyg. Chem. 28 (6), 291–304.
Ishidate, M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Food Chem. Toxicol. 22 (8), 623–636.
Isola, D., Smith, L.W., Ansari, R., Black, M.S., 2003b, March. Exposure characterization from a fragranced plug-in air freshener. Toxicol. Sci. 72. Great Clarendon St, Oxford OX2 6DP, England: Oxford Univ. Press, pp. 291–291.
Isola, D.A., Smith, L.W., Rogers, R.E., Black, M.S., 2003b. Exposure characterization of fragranced air fresheners. Allergy Clin. Immunol. Int. 139, 132–138.
Isola, D.A., Rogers, R.E., Myshaniuk, A., Jeng, C.J., Ansari, R., Smith, L.W., 2004. Exposure characterization from a surrogate fine fragrance. Toxicologist 78, 107.
Jansson, T., Curvall, M., Zech, L., 1985. Induction of sister-chromatid exchanges in human lymphocytes by neutral and phenolic constituents from the semi-volatile material of cigarette smoke condensate. Mutat. Res. Environ. Mutagen. Relat. Subj. 147 (5), 299.
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.
Jeong, S.-H., Kim, B.-Y., Kang, H.-G., Ku, H.-O., Cho, J.-H., 2005. Effects of butylated hydroxyanisole on the development and functions of reproductive system in rats. Toxicology 208 (1), 49–62.
Jimbo, Y., 1983. Penetration of fragrance compounds through human epidermis. J. Dermatol. 10 (3), 229–239.
Jimbo, Y., Ishihara, M., Osamura, H., Takano, M., Ohara, M., 1983. Influence of vehicles on penetration through human epidermis of benzyl alcohol, isoeugenol and methyl isoeugenol. J. Dermatol. 10, 241–250.
Kavlock, R.J., 1990. Structure-activity relationships in the developmental toxicity of substituted phenols: in vivo effects. Teratology 41 (1), 43–59.
Kono, M., Yoshida, Y., Itaya, Y., Shimobo, K., Yoshikawa, K., Terashita, T., Shishiyama, J., 1995. Antimicrobial Activity and Mutagenicity of Allyl Isothiocyanate and Several Essential Oils from Spices. Memoirs of the Faculty of Agriculture of Kinki University, Japan.
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.
Layton, K.A., Wolfe, G.W., Wang, Y., Bishop, J., Chaping, R.E., 2001. Reproductive effects of isoeugenol in Sprague-Dawley rats when assessed by the continuous breeding protocol. Toxicol. 60 (1), 384.
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.
Lewis-Burkey, J., Sauer, J.M., McQueen, C.A., Sipes, I.G., 2000. Cytotoxicity and genotoxicity of methyleugenol and related congeners—a mechanism of activation for methyleugenol. Mutat. Res. Fundam. Mol. Mech. Mutagen. 453 (1), 25–33.
Liu, F.C., Hotchkiss, S.A.M., 1996. In vitro percutaneous disposition of the cutaneous sensitizers eugenol and isoeugenol. In: Presented at the European Society of Contact Dermatitis/Jadassohn Centenary Congress, London.
Liu, F.C., Hotchkiss, S.A.M., 1997a. Comparative skin absorption, metabolism and protein binding of the sensitizers eugenol and isoeugenol. Unpublished. In: Presented at Eur. Res. Gp. On Exptl (Contact Dermatitis in Odense).
Liu, F.C., Hotchkiss, S.A.M., 1997b. 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., 1998. In vivo metabolism of eugenol and isoeugenol following topical application in male F344 rats. Br. J. Clin. Pharmacol. 45 (5), 506–507.
Madsen, J.T., Vogel, S., Johansen, J.D., Sorensen, J.A., Andersen, K.E., Nielsen, J.B., 2011. Percutaneous penetration characteristics and release kinetics of contact allergens encapsulated in ethosomes. Cutan. Ocul. Toxicol. 30 (1), 38–44.
Maralhas, A., Monteiro, A., Martins, C., Kranendonk, M., Laires, A., Rueff, J., Rodrigues, A.S., 2006. Genotoxicity and endoreduplication inducing activity of the food flavouring eugenol. Mutagenesis 21 (3), 199–204.
Maura, A., Pino, A., Ricci, R., 1989. Negative evidence in vivo of DNA-damaging, mutagenic and chromosomal effects of eugenol. Mutat. Res. Lett. 227 (2), 125–129.
Martins, C., Doran, C., Laires, A., Rueff, J., Rodrigues, A.S., 2011. Genotoxic and apoptotic activities of the food flavourings myristicin and eugenol in AA8 and XRCC1 deficient EM9 cells. Food Chem. Toxicol. 49 (2), 385–392.
Meredith, C., Massey, E., Minet, E., 2009. In vitro characterization of hepatic eugenol and methyleugenol bioactivation versus detoxification pathways. Toxicol. 108 (1), 55.
Meyer, F., Meyer, E., 1959. Absorption of ethereal oils and substances contained in them through the skin. Arzneim. Drug. Res. 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. Cancer Res. 43 (3), 1124–1134.
Miller, D., Wheals, B.B., Beresford, N., Sumpter, J.P., 2001. Estrogenic activity of phenolic additives determined by an in vitro yeast bioassay. Environ. Health Perspect. 109 (2), 133.
Miller, E.G., Washington, V.H., Bowies, W.H., Zimmermann, E.R., 1986. Mutagenic potential of some chemical components of dental materials. Dent. Mater. 2 (4), 163–165.
Miyazaki, Y., Motohashi, Y., Kobayashi, S., 1992. Changes in mood by inhalation of essential oils in humans. 2. Effect of essential oils on blood-pressure, heart-rate, RR intervals, performance, sensory evaluation and POMS. Mokuzai Gakkaishi 38 (10), 909–913.
Mulky, N., Amonkar, A.J., D'Souza, A.V., Bhide, S.V., 1987. Antimutagenicity of curcumins and related compounds: the structural requirement for the antimutagenicity of curcumins. Indian Drugs 25, 91–95.
Myhr, B.C., Caspary, W.J., Holden, H.E., 1991. Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: results for 31 coded compounds in the National Toxicology Program. Environ. Mol. Mutagen. 18 (1), 51–83.
National Toxicology Program, 1983. Carcinogenesis Studies of Eugenol in F344/N Rats and B6C3F1 Mice (Feed Studies) (Unpublished).
National Toxicology Program, 1999. Final Report on the Developmental Toxicity of Isoeugenol (CAS # 97-54-1) in Sprague-Dawley CD(r)rats Exposed on Gestation Days 6-19. NTP-TER-97-006.
National Toxicology Program, 2002. Isoeugenol: Reproductive Assessment by Continuous Breeding when Administered to Sprague-Dawley Rats by Gavage. NTP-RACB-97-004; TherImmune Research Corporation Study No. 7244–203.
Nestmann, E.R., Lee, E.G., 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.
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), 273–280.
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.
Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978. Mutagenicity of food flavours in bacteria (1st Report). In: Osaka-furitsu Koshu Eisei Kenkyu Hokoku Shokuhin Eisei Hen, 9, pp. 177–181.
OECD, 2012. The OECD QSAR Toolbox, V. 3.1. 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.
Perrucci, S., Macchioni, G., Cioni, P.L., Flamini, G., Morelli, I., 1995. Structure/activity relationship of some natural monoterpenes as acaricides against *Psoroptes cuniculi*. J. Nat. Prod. 58 (8), 1261–1264.
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. Int. Rep. 64, 1–12.
Phillips, D.H., Reddy, M.V., Randerath, K., 1984. 32P-post-labelling analysis of DNA adducts formed in the livers of animals treated with safrole, estragole and other naturally-occurring alkenylbenzenes. II. Newborn male B6C3F1 mice. Carcinogenesis 5 (12), 1623–1628.
Phillips, D.H., 1990. Further evidence that eugenol does not bind to DNA in vivo. Mutat. Res. Lett. 245 (1), 23–26.
Ørstavik, D., Hongslo, J.K., 1985a. Mutagenicity of endodontic sealers. Biomaterials 6 (2), 129–132.
Ørstavik, D., Hongslo, J.K., 1985b. Mutagenicity of endodontic sealers. Biomaterials 6 (2), 129–132.
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.
Randerath, K., Haglund, R.E., Phillips, D.H., Reddy, M.V., 1984. 32P-post-labelling analysis of DNA adducts formed in the livers of animals treated with safrole, estragole and other naturally-occurring alkenylbenzenes. I. Adult female CD-1 mice. Carcinogenesis 5 (12), 1613–1622.
Rapson, W.H., Nazar, M.A., Butsky, V.V., 1980. Mutagenicity produced by aqueous chlorination of organic compounds. Bull. Environ. Contam. Toxicol. 24 (1), 590–596.
Regnault-Roger, C., Hamraoui, A., 1995. Fumigant toxic activity and reproductive inhibition induced by monoterpenes on *Acanthoscelides obtectus* (Say)(Coleoptera), a bruchid of kidney bean (*Phaseolus vulgaris* L.). J. Stored Prod. Res. 31 (4), 291–299.
Reus, A.A., Usta, M., Krul, C.A., 2012. The use of ex vivo human skin tissue for genotoxicity testing. Toxicol. Appl. Pharmacol. 261 (2), 154–163.
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), 1977. Doctoral Dissertation: the Comparative Respiratory Irritation Potential of Fourteen Fragrance Raw Materials. RIFM report number 9011. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1981. Rat Topical Application Photoirritation Test with Eugenol. Unpublished report from Quest International. RIFM report number 45998. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1980. Ames metabolic Activation Test to Assess the Potential Mutagenic Effect of Eugenol. Unpublished report from Quest International. RIFM report number 46001. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1994a. The Ultimate Biodegradability of Eugenol in the Sealed Vessel Test. Unpublished report from Quest International Ltd.. RIFM report number 34944. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1994b. Partition Coefficient N-octanol/water of Eugenol. Unpublished Report from Givaudan. RIFM report number 51239. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1996. [Submission to EPA] Dermal Penetration Potential of Perfume Materials, with Letter Dated 5/28/96. Unpublished report from Procter and Gamble Company. RIFM report number 33463. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1997. Investigation of Oxidation Gases from Paraffin Aromatic Candles in Toxicological Relevance to Classes of Damaging Materials. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from the Union of German Candle Manufacturers. RIFM report number 18011.
RIFM (Research Institute for Fragrance Materials, Inc), 1999. Investigation of the Ecological Properties of Eugenol. Unpublished report from Haarmann and Reimer GmbH. RIFM report number 37173. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2001. Repeated Insult Patch Test of Eugenol in Human Subjects. RIFM report number 39081. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2003a. Airborne Levels of Selected Fragrance Materials in a Simulated Bathroom. RIFM report number 41708. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2003b. Indoor Air Quality Evaluation of a Plug-in Air Freshener. RIFM report number 43292. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2004. Airborne Levels of Selected Fragrance Materials Following a Controlled Exposure to a Surrogate Fine Fragrance. RIFM report number 47425. RIFM, Woodcliff lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2010a. Partition Coefficient N-octanol/water of Eugenol (Eugenol Pure Cosmos). Unpublished report from Givaudan. RIFM report number 61357. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2010b. Toxicology and Carcinogenesis Studies of Isoeugenol (CAS No. 97-54-1) in F344/N Rats and B6C3F1 Mice (Gavage Studies). Unpublished report from the National Toxicology Program. RIFM report number 605. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2012. A Two-week Inhalation Toxicity Study of Aerolized Isoeugenol in the Sprague Dawley Rat. RIFM report number 64243. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Use Level Survey, May, 2013.
Robin, O., Alaoui-Ismaili, O., Dittmar, A., Vernet-Maury, E., 1998. Emotional responses evoked by dental odors: an evaluation from autonomic parameters. J. Dent. Res. 77 (8), 1638–1646.
Rockwell, P., Raw, I., 1979. A mutagenic screening of various herbs, spices, and food additives. Nutr. Cancer 1 (4), 10–15.
Rogers, R.E., Isola, D.A., Smith, L.W., 2003. Characterization of potential human exposure to fragrances during consumer product use. J. Allergy Clin. Immunol. 111 (2), S239.
Rogers, R.E., Isola, D.A., Jeng, C.J., Lefebvre, A., Smith, L.W., 2005. Simulated inhalation levels of fragrance materials in a surrogate air freshener formulation. Environ. Sci. Technol. 39 (20), 7810–7816.
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., Steinhuis, W.H., De Vogel, N., Van Osenbruggen, W.A., Schouten, A., Verhagen, H., 1995b. Antimutagenicity of eugenol in the rodent bone marrow micronucleus test. Mutat. Res. Lett. 346 (2), 69–75.
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., 1995c. Effect of short-term dietary administration of eugenol in humans. In: Modulation of Biotransformation and Genotoxicity by Eugenol, pp. 117–130 (Chapter 7).
Rompelberg, C.J.M., Steinhuis, W.H., De Vogel, N., Van Osenbruggen, W.A., Schouten, A., Verhagen, H., 1995e. Antimutagenicity of eugenol in the rodent bone marrow micronucleus test. In: Modulation of Biotransformation and Genotoxicity by Eugenol, pp. 87–97. Chapter 5.
Rompelberg, C.J.M., Evertz, S.J.C.J., Bruijntjesrozier, G.C.D.M., Van den Heuvel, P.D., Verhagen, H., 1996a. Effect of eugenol on the genotoxicity of established mutagens in the liver. Food Chem. Toxicol. 34 (1), 33–42.
Rompelberg, C.J.M., Evertz, S.J.C.J., Bruijntjesrozier, G.C.D.M., Van den Heuvel, P.D., Verhagen, H., 1995d. Effect of eugenol on the genotoxicity of established

mutagens in the liver. In: Modulation of Biotransformation and Genotoxicity by Eugenol, pp. 69–86. Chapter 4.
Rompelberg, C.J.M., Vogels, J.T.W.E., de Vogel, N., Bruijntjes-Rozier, G.C.D.M., Stenhuis, W.H., Bogaards, J.J.P., Verhagen, H., 1996b. Effect of short-term dietary administration of eugenol in humans. Hum. Exp. Toxicol. 15 (2), 129–135.
Rompelberg, C.J.M., Steenwinkel, M.S., van Asten, J.G., van Delft, J.H.M., Baan, R.A., Verhagen, H., 1996c. Effect of eugenol on the mutagenicity of benzo [a] pyrene and the formation of benzo [a] pyrene-DNA adducts in the λ-lacZ-transgenic mouse. Mutat. Res. Genet. Toxicol. 369 (1), 87–96.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., Mahony, C.O., 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.
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.
Sasaki, Y., Imanishi, H., Ohta, T., Shirasu, Y., 1989. Modifying effects of components of plant essence of the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells. Mutat. Res. Lett. 226 (2), 103–110.
Schiestl, R.H., Chan, W.S., Gietz, R.D., Mehta, R.D., Hastings, P.J., 1989. Safrole, eugenol and methyleugenol induce intrachromosomal recombination in yeast. Mutat. Res. Genet. Toxicol. 224 (4), 427–436.
Schiestl, R.H., 1993. Nonmutagenic carcinogens induce intrachromosomal recombination in dividing yeast cells. Environ. health Perspect. 101 (Suppl. 5), 179.
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.
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.
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.
Schunk, H.H., Shibamoto, T., Tan, H.K., Wei, C.I., 1988. Biological and chemical studies on photochemical products obtained from eugenol, benzyl acetate and benzyl benzoate. Dev. food Sci.
Sekizawa, J., Shibamoto, T., 1982. Genotoxicity of safrole-related chemicals in microbial test systems. Mutat. Res. Genet. Toxicol. 101 (2), 127–140.
Seto, T.A., Keup, W., 1969. Effects of alkylmethoxybenzene and alkylmethylenedioxybenzene essential oils on pentobarbital and ethanol sleeping time. Arch. Int. Pharmacodyn. 180 (1), 232–240.
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 (12), 164–176.
Singal, M., Randazzo, J., Kirkpatrick, D., Burleson, F.G., Vitale, D., 2013. Evaluation of nose-only inhalation exposure to aerosolized isoeugenol in Sprague-Dawley rats. Toxicol. 32 (1), 331.
Smith, L.W., Rogers, R.E., Black, M.S., Isola, D.A., 2004, June. Exposure characterizations of three fragranced products. Toxicol. Appl. Pharmacol. 197 (3), pp. 189–189, 525 B ST, STE 1900, San Diego, CA 92101-4495 USA: Academic Press Inc Elsevier Science.
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., 1981a. The action of transition metals on the genotoxicity of simple phenols, phenolic acids and cinnamic acids. Cancer Lett. 14 (3), 251–260.
Stich, H.F., Stich, W., Lam, P.P.S., 1981b. Potentiation of genotoxicity by concurrent application of compounds found in betel quid: arecoline, eugenol, quercetin, chlorogenic acid and Mn 2+. Mutat. Res. Genet. Toxicol. 90 (4), 355–363.
Storer, R.D., McKelvey, T.W., Kraynak, A.R., Elia, M.C., Barnum, J.E., Harmon, L.S., DeLuca, J.G., 1996. Revalidation of the in vitro alkaline elution/rat hepatocyte assay for DNA damage: improved criteria for assessment of cytotoxicity and genotoxicity and results for 81 compounds. Mutat. Res. Genet. Toxicol. 368 (2), 59–101.
Sukumaran, K., Kuttan, R., 1995. Inhibition of tobacco-induced mutagenesis by eugenol and plant extracts. Mutat. Res. Genet. Toxicol. 343 (1), 25–30.
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.
Sutton, J.D., 1986. Metabolic Studies of Eugenol in Relation to its Safety Evaluation. Doctorial Dissertation (Unpublished. A thesis submitted for the degree of Doctor of Philosophy in the University of London).
Swanson, A.B., Miller, E.C., Miller, J.A., 1978. Metabolism of naturally occurring arylalkenes to mutagenic epoxides. Fed. Proc. Abstr. 37 (6), 1383.
Swanson, A.B., Chambliss, D.D., Blomquist, J.C., Miller, E.C., Miller, J.A., 1979. The mutagenicities of safrole, estragole, eugenol, trans-anethole, and some of their known or possible metabolites for Salmonella typhimurium mutants. Mutat. Res. Fundam. Mol. Mech. Mutagen. 60 (2), 143–153.
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. Biochem. Biophys. 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.
Telford, I.R., Woodruff, C.S., Linford, R.H., 1962. Fetal resorption in the rat as influenced by certain antioxidants. Am. J. Anat. 110, 29–36.
Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Anderson, B., 1987. Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. Science 236 (4804), 933–941.
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., 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.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.
To, L.P., Hunt, T.P., Andersen, M.E., 1982. Mutagenicity oftrans-anethole, estragole, eugenol, and safrole in the Ames *Salmonella typhimurium* assay. Bull. Environ. Contam. Toxicol. 28 (6), 647–654.
Tsutsui, T., Suzuki, N., Kobayashi, Y., Suzuki, H., Fukuda, S., Maizumi, H., 1987, January. Assessment of the carcinogenic hazard of 27 substances used in dental practices. Jpn. J. Pharmacol. 43 pp. P132–P132, Editorial Off, Kantohya Bldg Gokomachi-Ebisugawa Nakagyo-Ku, Kyoto 604, Japan: Japanese Pharmacological Soc.
USEPA, 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, V. 4.11. United States Environmental Protection Agency, Washington, DC, USA.
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.
VanDuuren, B.L., Goldschmidt, B.M., 1976. Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. J. Natl. Cancer Inst. 56 (6), 1237–1242.
Vethanayagam, D., Vliagoftis, H., Mah, D., Beach, J., Smith, L., Moqbel, R., 2013. Fragrance materials in asthma: a pilot study using a surrogate aerosol product. J. Asthma 50 (9), 975–982.
Vishteh, A., Thomas, I., Imamura, T., 1986. Eugenol modulation of the immune response in mice. Immunopharmacology 12, 187–192.
Vorhees, C.V., Butcher, R.E., Brunner, R.L., Wootten, V., Sobotka, T.J., 1981. Developmental neurobehavioral toxicity of butylated hydroxyanisole (BHA) in rats. Neurobehav. Toxicol. Teratol. 3, 321–329.
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. Fundam. 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.
Woolverton, C.J., Fotos, P.G., Mokas, M.J., Mermigas, M.E., 1986a. Evaluation of eugenol for mutagenicity by the mouse micronucleus test. J. Oral Pathol. Med. 15 (8), 450–453.
Woolverton, C.J., Fotos, P.G., 1986b. Examination of eugenol mtuagenicity utilizing the mouse micronucleus test. J. Dent. Res. 65, 789.
Wurtzen, G., Olsen, P., 1986. BHA study in pigs. Food Chem. Toxicol. 24 (1), 1229–1233.
Yasunaga, K., Kiyonari, A., Oikawa, T., Abe, N., Yoshikawa, K., 2004. Evaluation of the Salmonella umu test with 83 NTP chemicals. Environ. Mol. Mutagen. 44 (4), 329–345.
Yoshimura, H., Nakamura, M., Koeda, T., 1981. Mutagenicity screening of anesthetics for fishes. Mutat. Res. Genet. Toxicol. 90 (2), 119–124.
Zhao, K., Singh, J., 1998. Mechanisms of percutaneous absorption of tamoxifen by terpenes: eugenol, d-limonene and menthone. J. Control. Release 55, 253–260.

Further readings

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.