Food and Chemical Toxicology 161 (2022) 112872

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, 2-methoxy-4-vinylphenol, CAS Registry Number 7786-61-0

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ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Conflicts of interest

The authors declare that they have no conflicts of interest.

Version: 092721. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety

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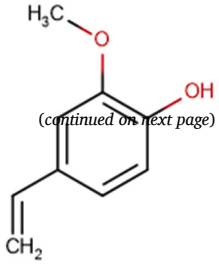
Name: 2-Methoxy-4-vinylphenol
CAS Registry Number: 7786-61-0



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https://doi.org/10.1016/j.fct.2022.112872
Received 27 September 2021; Received in revised form 30 November 2021; Accepted 14 February 2022
Available online 18 February 2022

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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable 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.

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2-Methoxy-4-vinylphenol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog isoeugenol (CAS # 97-54-1) show that 2-methoxy-4-vinylphenol is not expected to be genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on target data and date on analog isoeugenol (CAS # 97-54-1); 2-methoxy-4-vinylphenol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure to 2-methoxy-4-vinylphenol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2-methoxy-4-vinylphenol 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.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 1983a; NTP, 2010; EFSA, 2010)
Repeated Dose Toxicity: NOAEL = 37.5 mg/kg/day.	NTP (2010)
Reproductive Toxicity: NOAEL = 230 mg/kg/day.	NTP (2002)
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(RIFM, 2015; Kaidbey and Kligman, 1980; RIFM, 1979)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Screening-level: 2.86 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 13.96 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: LC50: 135.7 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: LC50: 135.7 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.1357 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 2-Methoxy-4-vinylphenol
2. **CAS Registry Number:** 7786-61-0
3. **Synonyms:** 4-Hydroxy-3-methoxystyrene; Phenol, 4-ethenyl-2-methoxy-; *p*-Vinylcatechol-o-methyl ether; *p*-Vinylguaiacol; Varmol 106; 2-Methoxy-4-vinylphenol
4. **Molecular Formula:** $C_9H_{10}O_2$
5. **Molecular Weight:** 150.17
6. **RIFM Number:** 6220
7. **Stereochemistry:** There is no stereocenter possible, and no stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 247.07 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 2.05 (Smith et al., 2002), 2.24 (EPI Suite)
4. **Melting Point**: 50.12 °C (EPI Suite)
5. **Water Solubility:** 926 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00424 mm Hg at 20 °C (EPI Suite v4.0), 0.0077 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** Absorbance in the range of 290–700 nm, with peak absorbance at 270 nm and returning to baseline by 330 nm. Molar absorption coefficients of 570, 833, and 1745 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively. Molar absorption coefficient under basic conditions is above the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless or pale straw-colored oily liquid solidifying in the cold. Powerful, spicy, clove-like odor with a penetrating, warm but also somewhat tarry undertone and good tenacity (Arctander, 1969).

3. Volume of use (Worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0012% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0000042 mg/kg/day or 0.00034 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00048 mg/kg/day (RIFM, 2019)

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

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

5. Derivation of systemic absorption

1. **Dermal:** 38.4%

Liu and Hotchkiss, 1997: 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 isoeugenol (CAS # 97-54-1) was applied to the skin of 3 F344 rats for 24 h. The absorption through the skin was 36.6 ± 0.6% to 48.7 ± 9.34% of the applied dose. Radioactive urinary metabolites recovered were 25.0 ± 1.0% of the dose. An *in vitro* skin absorption study was conducted using human skin. Radiolabeled [14C-methoxy] isoeugenol in ethanol was applied to freshly excised human skin at a dose of 92.2 μg/cm^2 from 3 volunteers under unoccluded conditions for 72 h in diffusion cells. After 72 h, radioactivity was measured in the skin, on the skin surface, and in the receptor fluid. Recovery of radioactivity as a percent of the dose was 30.0 ± 9.3% in the receptor fluid and 8.4 ± 3.5% in the skin. Total uptake was 38.4% ± 12.6%, and the total recovery was 60.1 ± 7.3%. No detectable metabolism was seen in the skin.

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

6. Computational toxicology evaluation

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

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

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

7. Metabolism

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

8. Natural occurrence

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

Asafoetida oil
Coffee
Curry (*Bergera koenigii* L.)
Fish
Lovage (*Levisticum officinale* Koch)
Maize (*Zea mays* L.)
Pork
Salvia species
Vanilla
Wine

*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. This is a partial list.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 04/26/21.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic or clastogenic activity of 2-methoxy-4-vinylphenol; however, read-across can be made to isoeugenol (CAS # 97-54-1; see Section VI).

The mutagenic activity of isoeugenol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in an equivalent manner with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with

isoeugenol in dimethyl sulfoxide (DMSO) at concentrations up to 150.00 μL/plate (162000 μg/plate). No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1983a). Under the conditions of the study, isoeugenol was not mutagenic in the Ames test, and this can be extended to 2-methoxy-4-vinylphenol.

The clastogenicity of isoeugenol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovary cells were treated with isoeugenol in DMSO at concentrations up to 200 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (NTP, 2010). Under the conditions of the study, isoeugenol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to 2-methoxy-4-vinylphenol.

To further verify the results of the *in* vitro chromosome aberration study, the clastogenic activity of isoeugenol 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 via oral gavage (solvent not specified) to groups of male mice (strain not specified). Doses of 500, 1000, or 2000 mg/kg were administered. Mice from each dose level were euthanized 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 (EFSA, 2010). Under the conditions of the study, isoeugenol was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to 2-methoxy-4-vinylphenol.

Due to only using male mice in the prior *in vivo* micronucleus test, the clastogenic activity of isoeugenol was evaluated in a second *in vivo* micronucleus test conducted in compliance with GLP regulations and in an equivalent manner with OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female B6C3F1 mice. Doses of 37.5, 75, 150, 300, or 600 mg/kg body weight were administered. Peripheral blood samples were obtained from mice from each dose level after 3 months and examined for micronucleated erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated erythrocytes in the peripheral blood in male B6C3F1 mice; however, it did induce a statistically significant increase in the incidence of micronucleated erythrocytes in the peripheral blood in female B6C3F1 mice (NTP, 2010). A 3.2-fold increase of micronucleated erythrocytes was observed at 600 mg/kg body weight, and a significant dose-response was observed. Under the conditions of the study, isoeugenol was considered to be clastogenic in the *in vivo* micronucleus test in female B6C3F1 mice.

Though the second *in vivo* micronucleus test resulted in a positive result in female mice, there are numerous weaknesses in the study. As noted in the EFSA Scientific Opinion on Flavouring Group Evaluation 81, the second *in vivo* micronucleus test lacked a positive control, historical control data, and consistency in the control data sets between sexes, and the data provided on the ratios of micronucleated normochromatic erythrocytes per thousand normochromatic erythrocytes together with their standard errors appeared to be random (EFSA, 2010). Due to this, the clastogenic activity of isoeugenol was evaluated in a third *in vivo* micronucleus test conducted in compliance with GLP regulations and in an equivalent manner with OECD TG 474. The test material was administered via oral gavage (solvent not specified) to groups of male and female mice (strain not specified). Two doses 24 h apart of 500, 1000, and 2000 mg/kg body weight were administered to male mice, and 2 doses 24 h apart of 500, 1000, and 1500 mg/kg body weight were administered to female mice. Mice from each dose level were euthanized 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 (EFSA, 2010). Under the conditions of the study, isoeugenol was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to 2-methoxy-4-vinylphenol.

Most of the data available have negative results. However, in one study where a positive outcome in female animals was observed had significant drawbacks as listed above and hence cannot be considered as a biologically relevant outcome. Hence, it can be concluded that isoeugenol does not present a concern for genotoxic potential, and this can be extended to 2-methoxy-4-vinylphenol.

Additional References: Tennant et al., 1987; Azizan and Blevins, 1995; Sukumaran and Kuttan, 1995; Douglas et al., 1980; Green (1975); Ishidate (1982); Orstavik and Hongslo, 1985; Schiestl et al., 1989; Schunk et al., 1986; Rompelberg et al., 1995a; Mulky et al., 1987; RIFM, 1980a; NTP, 1983; Dorange et al., 1977; To et al., 1982; Yoshimura et al., 1981; Eder et al., 1980; Eder et al., 1982a; Eder et al., 1982b; Rapson et al., 1980; Green and Savage, 1978; Swanson et al., 1979; Haworth et al., 1983; Ishidate et al., 1984; Nestmann et al., 1980; Nestmann and Lee, 1983; Kono et al., 1995; Sekizawa and Shibamoto, 1982; Florin et al., 1980; Rockwell and Raw, 1979; Pool and Lin, 1982; Stich et al., 1981a; Maralhas et al., 2006; Hayashi et al., 1984; Hayashi et al., 1988; Martins et al., 2011; Fowler et al., 2012; Hughes et al., 2012; Reus et al., 2012; Phillips et al., 1984; Someya et al., 2008; Lida, 2007; Stich et al., 1981b; Yoshimura et al., 1981; Randerath et al., 1984; Foureman et al., 1994; Yasunaga et al., 2004; Hikiba et al., 2005; Oda et al., 1978; Woolverton and Fotos, 1986a; Rompelberg et al., 1995a; Rompelberg et al., 1995b; Lewis-Burkey et al., 2000; Abraham (2001); Schiestl et al., 1989; Phillips (1990); Maura et al., 1989; Galloway et al., 1987; Tsutsui et al., 1987; Ohshima et al., 1989; Sasaki et al., 1989; Howes et al., 1990a; Jansson et al., 1985; Jansson et al., 1986; Fukuda (1987); Woolverton et al., 1986b; Myhr and Caspary, 1991; Rompelberg et al., 1995c; Bean and Galloway, 1993; Schiestl (1993); Ellahuene et al., 1994; Tennant et al., 1987; Howes et al., 1990b; Elmore and Fitzgerald, 1990; Armstrong et al., 1992; Bean et al., 1992; Allavena et al., 1992; Rompelberg et al., 1996a; Storer et al., 1996; Rompelberg et al., 1995d; Rompelberg et al., 1996b; Rompelberg et al., 1996c; Rompelberg et al., 1995a; Burkey et al., 1998; Bodell et al., 1998; RIFM, 1980b.

Literature Search and Risk Assessment Completed On: 04/23/21.

11.1.2. Repeated dose toxicity

The MOE for 2-methoxy-4-vinylphenol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose data on 2-methoxy-4-vinylphenol. There are numerous repeated dose studies conducted with read-across material isoeugenol (CAS # 97-54-1). Isoeugenol in corn oil was administered by oral gavage at doses of 0, 37.5, 75, 150, 300, or 600 mg/kg body weight/day, 5 days/week for 14 weeks to B6C3F1 mice and F344/N rats (10/sex/dose). The NOAEL for repeated dose toxicity was determined to be 37.5 mg/kg/day from a gavage 13-week subchronic toxicity study conducted in mice, in which no adverse effects were observed (NTP, 2010). Further, a 2-year chronic toxicity study was conducted. Groups of 50 male and 50 female B6C3F1 mice and F344/N rats were orally dosed via gavage with isoeugenol at 0, 75, 150, or 300 mg/kg body weight/day in corn oil 5 days/week for 105 weeks. When tested at the higher dosage of 75 mg/kg/day in a gavage 2-year carcinogenicity study, liver histopathological changes and hepatocarcinogenesis were observed in male mice (NTP, 2010). **Therefore, the MOE is equal to the isoeugenol NOAEL in mg/kg/day divided by the total systemic exposure, 37.5/0.00048, or 78125.**

The Expert Panel for Fragrance Safety* and the FEMA Expert Panel have reviewed the carcinogenicity data on isoeugenol (Smith et al., 2009). The US NTP concluded that isoeugenol is hepatocarcinogenic in male mice at 75 mg/kg/day and equivocally carcinogenic in female

mice (histiocytic sarcoma) and male rats (thymoma, mammary gland carcinoma) at 300 mg/kg/day (NTP, 2010). The high incidence of hepatocellular adenomas, carcinomas, and adenomas and carcinomas (combined) in both control and treatment groups of male mice was indicative of sensitivity of the B6C3F1 male mouse liver to toxicity and further neoplastic changes. The pattern of neoplastic responses was also consistent with the historically high levels of background hepatocellular neoplasms in male B6CF1 mice. In addition, all dose groups of male B6C3F1 mice suffered chronic hepatic toxicity before developing liver adenomas or carconomas. Thus, the appearance of male B6C3F1 mouse liver tumors in a 2-year carcinogenesis study is not considered relevant to human risk, considering there is high and variable incidence of tumor in B6C3F1 mouse in treated and control groups. All dose groups of male B6C3F1 mice suffered chronic hepatic toxicity prior to the development of either liver adenomas or carcinomas, as evidenced by the results of the 90-day and 2-year studies. Hepatocellular adenomas and carcinomas also occurred late in the life span of male mice (Smith et al., 2009). It is reported that the increase in the incidence of tumors in male B6C3F1 mice reflects the impact of high-dose liver damage to an organ already prone to spontaneous development of liver neoplasms (Haseman et al., 1986; Haseman et al., 1990). The total systemic exposure to 2-methoxy-4-vinylphenol is 0.00048 mg/kg/day, which is more than 5357000 times lower than the lowest dose level of isoeugenol in the NTP carcinogenicity studies. This MOE is considered adequate.

In addition, the total systemic exposure to 2-methoxy-4-vinylphenol (0.48 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) of a Cramer Class I material) for the repeated dose toxicity endpoint at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/15/21.

11.1.3. Reproductive toxicity

The MOE for 2-methoxy-4-vinylphenol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no developmental data on 2-methoxy-4-vinylphenol. Read-across material isoeugenol (CAS # 97-54-1) has a gavage developmental toxicity study conducted in rats. Isoeugenol in corn oil was administered by oral gavage at doses of 0, 250, 500, or 1000 mg/kg body weight/day to pregnant Sprague Dawley CD rats (25/group) on gestation days (GDs) 6–19. There was no mortality. Clinical signs of toxicity included sedation, lethargy, and piloerection, primarily at 500 and 1000 mg/kg/day. A dose-related statistically significant decrease was seen in maternal bodyweight gain. A statistically significant decrease in food consumption was observed at 1000 mg/kg/day. A statistically significant decrease in body weight and a statistically significant increase in the incidence of non-ossified sternebra(e) were observed in fetuses of the 1000 mg/kg/day group. The NOAEL for developmental toxicity was determined 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). **Therefore, the MOE for developmental toxicity is equal to the isoeugenol NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.00048, or 1041667.**

There are no fertility data on 2-methoxy-4-vinylphenol. Read-across material isoeugenol (CAS # 97-54-1) has a gavage multigenerational continuous breeding study conducted in rats. Isoeugenol in corn oil was administered by oral gavage to Sprague Dawley rats (20 pairs/group) (F0) at doses of 0, 70, 230 or 700 mg/kg body weight/day from one week prior to mating to study day 179. . A statistically significant decrease in live male pups of the F1 generation and a statistically significant decrease in F1 pup weight were seen at 700 mg/kg/day. Mild reproductive toxicity was observed at 700 mg/kg/day, as noted by a decreased number of male pups per litter during the F0 cohabitation and decreased male and female pup weights during the F1 cohabitation. The NOAEL for fertility was determined 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 the F1 cohabitation (NTP, 2002). In an *in vitro* skin absorption study conducted using human skin, 38.4% of the applied dosage of isoeugenol was absorbed (Liu and Hotchkiss, 1997). **Therefore, the MOE for fertility is equal to the isoeugenol NOAEL in mg/kg/day divided by the total systemic exposure, 230/0.00048, or 479167.**

In addition, the total systemic exposure to 2-methoxy-4-vinylphenol (0.48 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) of a Cramer Class I material) for the reproductive toxicity endpoint at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/15/21.

11.1.4. Skin sensitization

Based on the existing data, 2-methoxy-4-vinylphenol is a sensitizer. However, it does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 2-methoxy-4-vinylphenol. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a Confirmation of No Induction in Humans test (CNIH), 2-methoxy-4-vinylphenol was tested on 49 volunteers. A fragrance material (not specified) structurally similar to the target material has been tested before, where a no-effect concentration in humans was determined to be 1%. Therefore, 1% (500 μg/cm^2) 2-methoxy-4-vinylphenol was used for the induction and challenge in this CNIH. Sensitization reactions were observed in 1/49 subjects (RIFM, 1983b). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 below provides the maximum acceptable concentrations for 2-methoxy-4-vinylphenol that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/16/21.

11.1.5. Phototoxicity/photoallergenicity

Based on *in vitro* study data, 2-methoxy-4-vinylphenol does not present a concern for phototoxicity. Based on human study data for the read-across material, isoeugenol (CAS # 97-54-1), 2-methoxy-4-vinylphenol does not present a concern for photoallergenicity.

11.1.5.1. Risk assessment. The available UV/Vis spectra (OECD TG 101) for 2-methoxy-4-vinylphenol demonstrate that this material absorbs in the region of 290–700 nm. The molar absorption coefficient for maximum absorbance between 290 and 700 nm, under basic conditions (pH 10 or greater), is above the benchmark of concern for phototoxic effects (Henry et al., 2009). In an *in vitro* 3T3 Neutral Red uptake assay, 2-methoxy-4-vinylphenol was not predicted to be phototoxic based on both mean photo effect and photo-irritation factors (RIFM, 2015). There are no suitable experimental photoallergenicity studies available for 2-methoxy-4-vinylphenol. The structurally similar material, isoeugenol

Table 1
Maximum acceptable concentrations for 2-methoxy-4-vinylphenol that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	3.3×10^{-5}%
2	Products applied to the axillae	0.0015%	6.7×10^{-5}%
3	Products applied to the face using fingertips	0.029%	4.5×10^{-5}%
4	Fine fragrance products	0.027%	0.0012%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	2.0×10^{-4}%
6	Products with oral and lip exposure	0.016%	0.010%
7	Products applied to the hair with some hand contact	0.056%	5.0×10^{-5}%
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	1.0×10^{-4}%
10	Household care products with mostly hand contact	0.19%	7.1×10^{-4}%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	0.13%

Note.
[b]No reported use.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

(CAS # 97-54-1), demonstrates a greater degree of UV absorbance than the target material and has sufficient study data to address photoallergenicity; as such, it is a suitable read-across analog. In human studies, 5% isoeugenol was not found to be phototoxic (RIFM, 1979; Kligman, 1980). In accompanying photoallergy studies, volunteers received induction applications of 5% isoeugenol and challenge applications of 1% isoeugenol. No photoallergic reactions were observed (RIFM, 1979; Kligman, 1980). Based on *in vitro* study data, 2-methoxy-4-vinylphenol does not present a concern for phototoxicity. Based on human study data for the read-across material, isoeugenol (CAS # 97-54-1), 2-methoxy-4-vinylphenol does not present a concern for photoallergenicity.

11.1.5.2. UV Spectra analysis. The available UV/Vis spectra (OECD TG 101) for 2-methoxy-4-vinylphenol demonstrate that this material absorbs in the region of 290–700 nm, with peak absorbance at 270 nm and returning to baseline by 330 nm. Molar absorption coefficients of 570, 833, and 1745 L mol^{-1} • cm^{-1} were found under neutral, acidic, and basic conditions, respectively. The molar absorption coefficient under basic conditions (1745 L mol^{-1} • cm^{-1}) is above 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: 04/15/21.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on 2-methoxy-4-vinylphenol. Based on the Creme RIFM Model, the inhalation exposure is 0.00034 mg/day. This exposure is 4117.6 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: 04/16/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-methoxy-4-vinylphenol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. 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-vinylphenol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 2-methoxy-4-vinylphenol 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 $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in

EPI Suite v4.11).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 2-methoxy-4-vinylphenol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

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

11.2.1.4. 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	2.2	2.2
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
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 0.1357 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 04/21/21.

12. Literature Search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/26/21.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112872.

Appendix

Read-across Justification

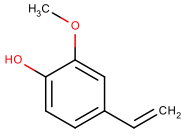
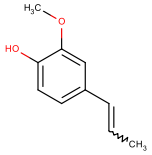
Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	135.7			1000000	0.1357	

Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	2-Methoxy-4-vinylphenol	Isoeugenol
CAS No.	7786-61-0	97-54-1
Structure		
Similarity (Tanimoto Score)		0.65
Endpoint		Genotoxicity Repeated dose toxicity Reproductive toxicity Photoallergenicity
Molecular Formula	$C_9H_{10}O_2$	$C_{10}H_{12}O_2$
Molecular Weight	150.18	164.20
Melting Point (°C, EPI Suite)	50.12	33.50
Boiling Point (°C, EPI Suite)	247.07	266.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.03	1.80
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	926.00	810.00
Log K_{OW}	2.24	3.04
J_{max} (μg/cm^2/h, SAM)	29.40	55.42
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.00	0.00
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Hydroquinones	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Hydroquinones
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	H-acceptor-path3-H-acceptor	H-acceptor-path3-H-acceptor
Oncologic Classification	Phenol-type Compounds	Phenol-type Compounds
Repeated Dose Toxicity		
Repeated Dose (HESS)	Styrene (Renal Toxicity) Alert	Curcumin (Renal toxicity) Alert
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Weak binder, OH group	Weak binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (moderate reliability)	Non-toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-methoxy-4-vinylphenol (CAS # 7786-61-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, isoeugenol (CAS # 97-

54-1) was identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Isoeugenol (CAS # 97-54-1) was used as a read-across analog for the target material 2-methoxy-4-vinylphenol (CAS # 7786-61-0) for the genotoxicity, repeated dose toxicity, reproductive toxicity, and photoallergenicity endpoints.
  - o The target material and the read-across analog belong to a class of alkyl phenols.
  - o The main difference between the target material and the read-across analog is that the target material has a vinyl substituent at para position, whereas the read-across analog has propenyl substituent at the para position.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have been alerted for undergoing Michael addition reactions and forming reactive hydroquinone. The data on the read-across confirm that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog, the *in silico* alert for the target material is superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
  - o The target material and the read-across analog do not have a chromophore that is expected to absorb in the UV/Vis range of the electromagnetic spectrum that is of interest to human health toxicity. Based on *in vitro* study data, the target material does not present a concern for phototoxicity. Based on the human study data for the read-across material, it does not present a concern for photoallergenicity. Therefore, the structural difference between the target material and the read-across analog is toxicologically insignificant for the phototoxicity endpoint, and the target material can be predicted not to cause any concern for photoallergenicity.

Research Institute for Fragrance Materials, Inc. **1**.

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