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Short Review

RIFM fragrance ingredient safety assessment, zingerone, CAS Registry Number 122-48-5

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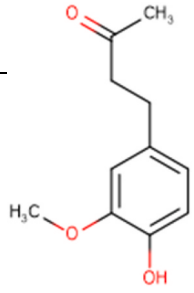
CAS Registry Number: 122-48-5



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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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017, 2024) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
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.

Zingerone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog guaiacol (CAS # 90-05-1) show that zingerone is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to zingerone is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog 2-methoxy-4-propylphenol (CAS # 2785-87-7) provided zingerone a No Expected Sensitization Induction Level (NESIL) of 1700 μg/cm^2 for the skin sensitization endpoint. The photoirritation endpoint was evaluated based on data and ultraviolet/visible (UV/Vis) spectra; zingerone is not photoirritating. The photoallergenicity endpoint was evaluated based on UV/Vis spectra; zingerone is not expected to be photoallergenic. The environmental endpoints were evaluated; zingerone was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2004; ECHA, 2010b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

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Skin Sensitization: NESIL = 1700 μg/cm^2.	RIFM (2015b)
Photoirritation/Photoallergenicity: Not photoirritating. Not expected to be photoallergenic.	(UV/Vis Spectra, RIFM Database; RIFM, 2015a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical Measured Value: 74% (OECD 301F)	RIFM (2002)
Bioaccumulation:	
Screening-level: 3.92 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 6453 mg/L	(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	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 6453 mg/L	(Salvito et al., 2002)
RIFM PNEC is: 6.453 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level	

1. Identification

1. **Chemical Name:** Zingerone
2. **CAS Registry Number:** 122-48-5
3. **Synonyms:** 2-Butanone, 4-(4-hydroxy-3-methoxyphenyl)-; 4-(4-Hydroxy-3-methoxyphenyl)-2-butanone; 4-Hydroxy-3-methoxybenzylacetone; 2-(4-Hydroxy-3-methoxyphenyl)ethyl methyl ketone; 3-Methoxy-4-hydroxybenzylacetone; Vanillylacetone; 4-(4-Hydroxy-3-methoxyphenyl)butan-2-one; Zingerone
4. **Molecular Formula:** $C_{11}H_{14}O_3$
5. **Molecular Weight:** 194.23 g/mol
6. **RIFM Number:** 1002
7. **Stereochemistry:** No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 310.81 °C (EPI Suite v4.11)
2. **Flash Point:** >200 °F; closed cup (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 0.4 (RIFM, 2000), 1.31 (EPI Suite v4.11)
4. **Melting Point**: 32 °C (RIFM, 2000), 91.71 °C (EPI Suite v4.11)
5. **Water Solubility:** 3571 mg/L at 25 °C (EPI Suite v4.11)
6. **Specific Gravity:** 1.138 (FMA)
7. **Vapor Pressure:** 0.000253 mm Hg (EPI Suite v4.11), <0.001 mm Hg at 20 °C (FMA)
8. **UV Spectra:** No absorbance between 290 and 700 nm under neutral and acidic conditions; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1}). Significant absorbance under basic conditions, with peak absorbance at 402 nm and returning to baseline by 470 nm. The molar absorption coefficient under basic conditions is 36,992 L mol^{-1} • cm^{-1}which is above the benchmark of concern.
9. **Appearance/Organoleptic:** Pale yellowish, pale amber-colored or cream-colored crystalline mass. Sweet-spicy, warm, heavy floral, mildly animal-balsamic, and vanilla-like odor with excellent tenacity. Sweet and spicy, balsamic vanilla-like taste in concentrations below 40 ppm. Slightly pungent-burning at higher concentrations, but not very pleasant above 100 ppm. The pleasant taste level is generally between 10 and 25 ppm, depending upon accompanying flavor materials (Arctander, 1969).

3. Volume of use (Worldwide band)

1 1–10 metric tons per year (IFRA, 2019)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.045% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000011 mg/kg/day or 0.00077 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00043 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, 2017; Safford et al., 2015, 2017, 2024).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 5. 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, 2017; Safford et al., 2015, 2017, 2024).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
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 v4.5 (OECD, 2021b)
I	I	I

2. Analogs Selected:

a. **Genotoxicity:** Guaiacol (CAS # 90-05-1); Weight of Evidence (WoE) - Acetophenone (CAS # 98-86-2)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 2-Methoxy-4-propylphenol (CAS # 2785-87-7); WoE - Acetophenone (CAS # 98-86-2)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

Zingerone is reported to occur in the following foods by the VCF*.

Capers (*Capparis spinoza*)	Ginger (*Zingiber* species)
Mangifera species	*Vaccinium* species
Raspberry, blackberry, and boysenberry	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.

9. REACH dossier

Zingerone has been pre-registered for 2010; no dossier is available as of 10/03/24.

10. Conclusion

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

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.13
2	Products applied to the axillae	0.039
3	Products applied to the face/body using fingertips	0.78
4	Products related to fine fragrances	0.73
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.18
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.18
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.18
5D	Baby cream, oil, talc	0.18
6	Products with oral and lip exposure	0.43
7	Products applied to the hair with some hand contact	1.5
8	Products with significant ano-genital exposure (tampon)	0.077
9	Products with body and hand exposure, primarily rinse off (bar soap)	1.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	5.1
10B	Aerosol air freshener	5.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	2.8
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For zingerone, the basis was a skin sensitization NESIL of 1700 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA/Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.4.1.

11. Summary

11.1. Human Health Endpoint Summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk Assessment. The mutagenic activity of zingerone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with zingerone in ethanol at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2004). Under the conditions of the study, zingerone was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of zingerone; however, read-across can be made to guaiacol (CAS # 90-05-1; see Section 6).

The clastogenic activity of guaiacol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female NMRI mice. Doses of 125, 250, or 500 mg/kg were administered. Mice from each dose level were euthanized at 24 and 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2010b). Under the conditions of the study, guaiacol was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to zingerone.

As additional WoE, the clastogenic activity of acetophenone (CAS # 98-86-2) was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474 (ECHA, 2010a). Under the conditions of the study, acetophenone was considered not to be clastogenic in the *in vivo* micronucleus test, and this can be extended to zingerone.

Based on the data available, guaiacol does not present a concern for genotoxic potential, and this can be extended to zingerone.

Table 1
Summary of existing data on 2-methoxy-4-propylphenol as a read-across for zingerone.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm^2	NOEL-HMT (induction) µg/cm^2	LOEL (induction) µg/cm^2	WoE NESIL[2] µg/cm^2	LLNA[3] Weighted Mean EC3 Value µg/cm^2	GPMT[4]	Buehler
Moderate	1771	5520	N/A	1700	1700 (6.8 %)	Positive	N/A
	In vitro Data[5]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Inconclusive	Positive	Positive		No alert found	Michael addition	Schiff base formation; Michael addition

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; EC3 = concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = Not Available.
[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
[2]WoE NESIL limited to 2 significant figures.
[3]Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).
[4]Studies conducted according to the OECD TG 406 are included in the table.
[5]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/01/23.

11.1.2. Repeated Dose Toxicity

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

11.1.2.1. Risk Assessment. There are no repeated dose toxicity data on zingerone or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure for zingerone (0.43 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/16/23.

11.1.3. Reproductive Toxicity

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

11.1.3.1. Risk Assessment. There are no reproductive toxicity data on zingerone or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure for zingerone (0.43 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/16/23.

11.1.4. Skin Sensitization

Based on the existing data on the target material, the read-across material 2-methoxy-4-propylphenol, and WoE material acetophenone, zingerone was assigned a NESIL of 1700 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section 10.

11.1.4.1. Risk Assessment. Limited data are available on the skin sensitization potential of zingerone. Therefore, a structurally related material, 2-methoxy-4-propylphenol (CAS # 2785-87-7; see Section 6), was used for the risk assessment of zingerone. The data on the read-across material are summarized in Table 1. Additionally, acetophenone (CAS # 98-86-2; see Section 6) was used as WoE. Zingerone and read-across material 2-methoxy-4-propylphenol are predicted *in silico* to be reactive with skin proteins directly, while WoE material acetophenone was predicted *in silico* to be non-reactive with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Read-across material 2-methoxy-4-propylphenol was found to be borderline in an *in vitro* direct peptide reactivity assay (DPRA) and positive in a KeratinoSens, a human cell line activation test (h-CLAT), and a U937-CD86 test (Natsch, 2013; Emter et al., 2010; Piroird et al., 2015). The results were evaluated following the OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a), and based on the 2 out of 3 Defined Approach, 2-methoxy-4-propylphenol is a sensitizer. In a murine local lymph node assay (LLNA), read-across material 2-methoxy-4-propylphenol was found to be sensitizing with an EC3 value of 6.8% (1700 μg/cm^2) (skin sensitization 002 wt of evidence, ECHA, 2016). In guinea pig maximization tests, read-across material 2-methoxy-4-propylphenol presented reactions indicative of sensitization at 100% (RIFM, 1989; RIFM, 1988; skin sensitization 004 wt of evidence, ECHA, 2016). In a guinea pig maximization test, WoE material acetophenone did not lead to skin sensitization reactions (Klecak et al., 1977). In 3 separate human maximization tests, no skin sensitization reactions were observed when zingerone, read-across material 2-methoxy-4-propylphenol, and WoE material acetophenone were tested at 5520 μg/cm^2, 5520 μg/cm^2, and 1380 μg/cm^2, respectively (RIFM, 1977a; RIFM, 1977b; RIFM, 1971). Additionally, in a Confirmation of No Induction in Humans test with 1.5% or 1771 μg/cm^2 of read-across material 2-methoxy-4-propylphenol in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 107 volunteers (RIFM, 2015b).

Based on the WoE from structural analysis, *in vitro* studies, animal studies, and human studies on the read-across material, WoE material, and the target material, zingerone was assigned a WoE NESIL of 1700 μg/cm^2 (Table 1). Section 10 provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020).

Additional References: Itoh (1982); Natsch (2007); Natsch (2008); Sharp (1978); Klecak (1979); RIFM, 1970; Klecak (1985).

Literature Search and Risk Assessment Completed On: 01/11/24.

11.1.5. Photoirritation/Photoallergenicity

Based on UV/Vis absorbance spectra at the biologically relevant neutral condition and *in vitro* study data, zingerone does not present a concern for photoirritation. Based on UV/Vis absorbance spectra at the biologically relevant neutral condition, zingerone does not present a concern for photoallergenicity.

11.1.5.1. Risk Assessment. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm under both the biologically relevant neutral condition and the acidic condition. The corresponding molar absorption coefficients are below the benchmark of concern for photoirritation and photoallergenicity (Henry, 2009). Absorbance under the basic condition between 290 and 700 nm was demonstrated, and the corresponding molar absorption coefficient was above the benchmark of concern. However, the basic condition in this assay is defined as pH 10 or greater and is not biologically relevant for our purposes, where the route of exposure is topical. In an *in vitro* 3T3 Neutral Red uptake assay, zingerone was not predicted to be photoirritating based on the mean photo effect (RIFM, 2015a). Based on the *in vitro* study data and the lack of absorbance at the biologically relevant neutral condition, zingerone does not present a concern for photoirritation. Based on the lack of absorbance at the biologically relevant neutral condition, zingerone does not present a concern for photoallergenicity.

11.1.5.2. UV Spectra Analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance between 290 and 700 nm under neutral and acidic conditions; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1}). Significant absorbance was observed under basic conditions, with peak absorbance at 402 nm and returning to baseline by 470 nm. The molar absorption coefficient under basic conditions is 36,992 L mol^{-1} • cm^{-}1, above the benchmark of concern (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/11/23.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for zingerone 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 zingerone. Based on the Creme RIFM Model, the inhalation exposure is

0.00077 mg/day. This exposure is 1818.2 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: 08/22/23.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level Assessment

A screening-level risk assessment of zingerone 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, zingerone 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 zingerone as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk Assessment. Based on the current VoU (IFRA, 2019), zingerone 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. **RIFM, 2002**: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. 100 mg/L of the test material was incubated for 28 days. Biodegradation of 74% was observed.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Zingerone has been pre-registered for REACH with no additional data at this time.

11.2.1.3. Risk Assessment Refinement. Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L)

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>6453</u>			1000000	6.453	

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

Exposure	Europe	North America
Log K_{ow} Used	0.4	0.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU 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 6.453 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: 08/16/23.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf

- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 10/03/24.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2024.115116.

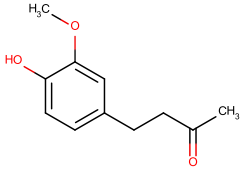
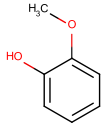
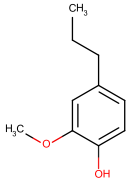
Appendix

Read-across Justification:

Methods

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

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

	Target Material	Read-across Material	Read-across Material	WoE Material
Principal Name	Zingerone	Guaiacol	2-Methoxy-4-propylphenol	Acetophenone
CAS No.	122-48-5	90-05-1	2785-87-7	98-86-2
Structure				
Similarity (Tanimoto Score)		0.33	0.80	0.28
SMILES	COc1cc(CCC(C)=O)ccc1O	COc1ccccc1O	CCCc1ccc(O)c(OC)c1	CC(=O)c1ccccc1

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	WoE Material
Endpoint		Genotoxicity (Clastogenicity)	Skin sensitization	Genotoxicity (Clastogenicity) Skin sensitization
Molecular Formula	$C_{11}H_{14}O_3$	$C_7H_8O_2$	$C_{10}H_{14}O_2$	C_8H_8O
Molecular Weight	194.23	124.139	166.22	120.151
Melting Point (°C, EPI Suite)	40.50	32.00	61.64	20.00
Boiling Point (°C, EPI Suite)	310.81	205.00	265.51	202.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.37E-02	1.37E+01	2.84E-01	5.29E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.57E+03	1.87E+04	2.28E+02	6.13E+03
Log KOW	1.31	1.32	2.87	1.58
J_{max} (μg/cm^2/h, SAM)	7.83	266.39	12.17	146.79
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.31E-06	1.22E-01	6.54E-03	1.05E+00
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found		No alert found
DNA Binding (OECD QSAR Toolbox v4.5)	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Alkyl phenols|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		No alert found
Carcinogenicity (ISS)	No alert found	No alert found		No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found		No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found		No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	H-acceptor-path3-H-acceptor	H-acceptor-path3-H-acceptor		No alert found
Oncologic Classification	Phenol-type Compounds	Phenol-type Compounds		Not classified
Skin Sensitization				
Protein Binding (OASIS v1.1)	No alert found		No alert found	No alert found
Protein Binding (OECD)	No alert found		No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found		No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Michael Acceptor identified.		Alert for Michael Acceptor identified.	No skin sensitization reactivity domain alerts identified.
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on zingerone (CAS # 122-48-5). 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, guaiacol (CAS # 90-05-1) and 2-methoxy-4-propylphenol (CAS # 2785-87-7) were identified as read-across analogs and acetophenone (CAS # 98-86-2) was identified as a WoE material with sufficient data for toxicological evaluation.

Conclusions

- Guaiacol (CAS # 90-05-1) was used as a read-across analog and acetophenone (CAS # 98-86-2) was used as a WoE material for the target material zingerone (CAS # 122-48-5) for the genotoxicity (clastogenicity) endpoint.
  - o The target material and the read-across analog share a commonality in that they are both phenols with a methoxy group.
  - o The key difference between the target material and the read-across analog is that the target material contains an aliphatic ketone not present in the read-across analog. Therefore, to satisfy the structural features of the target material, acetophenone (CAS # 98-86-2) is used as WoE. This chemical has an aliphatic ketone in the same position of the aromatic ring as the target material. The read-across analog, combined with the WoE material, contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.

- 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.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
- According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- Both the target material and read-across analog contain *in silico* alerts for Michael addition and p450-mediated activation to quinones (genotoxicity). The data from the genotoxicity (clastogenicity) section confirms that the read-across analog is not genotoxic. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the predictions are superseded by the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- 2-Methoxy-4-propylphenol (CAS # 2785-87-7) was used as a read-across analog, and acetophenone (CAS # 98-86-2) was used as a WoE material for the target material, zingerone (CAS # 122-48-5), for the skin sensitization endpoint.
  - The target material and the read-across analog share a commonality in that they are both phenols with ether functionality.
  - The key difference between the target material and the read-across analog is that the target material contains an aliphatic ketone not present in the read-across analog. Therefore, to satisfy the structural features of the target material, acetophenone (CAS # 98-86-2) is used as a WoE material. This chemical has an aliphatic ketone in the same position of the aromatic ring as the target material. The read-across analog, combined with the WoE material, contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and read-across analog contain an *in silico* alert for Michael acceptor (skin sensitization). However, the data from the skin sensitization section indicates that the material is a non-sensitizer. Therefore, the predictions are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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