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RIFM fragrance ingredient safety assessment, 3-methoxy-5-cresol, CAS Registry Number 3209-13-0

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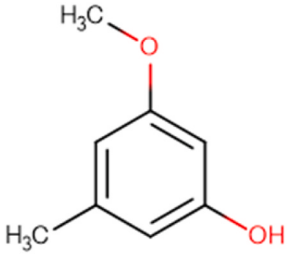

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Abbreviation/Definition List:

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., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic

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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.

3-Methoxy-5-cresol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from 3-methoxy-5-cresol and read-across analogs 3,5-dimethoxytoluene (CAS # 4179-19-5) and resorcinol (CAS # 108-46-3) show that 3-methoxy-5-cresol 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 3-methoxy-5-cresol is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from the target material and read-across analog 2-methoxy-4-methylphenol (CAS # 93-51-6) provided 3-methoxy-5-cresol a No Expected Sensitization Induction Level (NESIL) of 110 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 3-methoxy-5-cresol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-methoxy-5-cresol 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.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.
(RIFM, 2004b; RIFM, 2017a; ECHA REACH Dossier: Resorcinol; 1,3-benzenediol; ECHA, 2011)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 110 μg/cm^2. RIFM (1998)
Phototoxicity/Photoallergenicity: Not phototoxic and not expected to be photoallergenic.
(UV/Vis Spectra; RIFM Database; RIFM, 1975a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 89% (OECD 301F) RIFM (2000a)
Bioaccumulation:
Screening-level: 12.01 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: LC50: 1688 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: Fish LC50: 1688 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 1.688 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 3-Methoxy-5-cresol
2. **CAS Registry Number:** 3209-13-0
3. **Synonyms:** 3-Hydroxy-5-methoxytoluene; Phenol, 3-methoxy-5-methyl-; Orcinyl 3; 3-Methoxy-5-methylphenol; 3-Methoxy-5-cresol
4. **Molecular Formula:** $C_8H_{10}O_2$
5. **Molecular Weight:** 138.16 g/mol
6. **RIFM Number:** 5291
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 230.36 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 0.9 (RIFM, 2000b), 2.14 (EPI Suite)
4. **Melting Point**: 40.45 °C (EPI Suite)
5. **Water Solubility:** 4810 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0135 mm Hg at 20 °C (EPI Suite v4.0), 0.0239 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

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 v3.1.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0069% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.000011 mg/kg/day or 0.00083 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.00018 mg/kg/day (RIFM, 2021)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low.

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

6.2. Analogs selected

a. **Genotoxicity:** 3,5-Dimethoxytoluene (CAS # 4179-19-5) and resorcinol (CAS # 108-46-3)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 2-Methoxy-4-methylphenol (CAS # 93-51-6)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

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

8. Natural occurrence

3-Methoxy-5-cresol is not reported to occur in foods by the VCF*.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 12/13/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 3-methoxy-5-cresol 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)	0.0085
2	Products applied to the axillae	0.0025
3	Products applied to the face/body using fingertips	0.051
4	Products related to fine fragrances	0.047
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.012
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.012
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.012
5D	Baby cream, oil, talc	0.012
6	Products with oral and lip exposure	0.028
7	Products applied to the hair with some hand contact	0.096
8	Products with significant ano-genital exposure (tampon)	0.0050
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.092
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.33
10B	Aerosol air freshener	0.33
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.18
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

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 3-methoxy-5-cresol, the basis was a skin sensitization NESIL of 110 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 3-methoxy-5-cresol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 3-methoxy-5-cresol 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 3-methoxy-5-cresol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. A small increase in the mean number of revertant colonies was observed at 5000 μg/plate in strain TA1535 presence of S9 (RIFM, 2004a). However, this increase in

revertant colonies was not 3-fold greater than the solvent control and was within the historical control, so the increase was considered not biologically relevant. Under the conditions of the study, 3-methoxy-5--cresol was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 3-methoxy-5-cresol; however, read-across can be made to 3,5-dimethoxytoluene and resorcinol (CAS # 4179-19-5 and 108-46-3; see Section VI).

The clastogenic activity of 3,5-dimethoxytoluene was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 3,5-dimethoxytoluene in DMSO at concentrations up to 1520 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 450 μg/mL in the presence and absence of metabolic activation. 3,5-Dimethoxytoluene did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2017a). Under the conditions of the study, 3,5-dimethoxytoluene was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 3-methoxy-5-cresol.

The clastogenic activity of resorcinol was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with resorcinol (solvent not specified), and micronuclei analysis was conducted at concentrations up to 1100 μg/mL in the presence and absence of metabolic activation. Resorcinol did induce binucleated cells with micronuclei when tested in the presence and absence of an S9 activation system (ECHA, 2011). Increases in the binucleated cells with micronuclei frequency were observed in the 3-h treatment with S9, where treatment commenced 24 h post mitogen stimulation and in the 20-h treatment without S9, where treatment commenced either 24 or 48 h following mitogen stimulation. Under the conditions of the study, resorcinol was considered to be clastogenic in the *in vitro* micronucleus test, and this can be extended to 3-methoxy-5-cresol.

In addition to the *in vitro* micronucleus test, numerous *in vitro* chromosome aberration studies were conducted, and the results were mixed (ECHA, 2011). To further investigate and clarify the results of these *in vitro* tests, an *in vivo* micronucleus test was conducted.

The clastogenic activity of resorcinol 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 water via oral gavage to groups of male and female Sprague Dawley rats. Doses of 125, 250, and 500 mg/kg body weight were administered. Rats from each dose level were euthanized at 48 h and the bone marrow was extracted and examined for polychromatic erythrocytes. Bone marrow exposure was confirmed due to cytotoxicity observed in female rats at 500 mg/kg. Systematic exposure was confirmed through plasma analysis of the test animals after oral administration to doses of 80 and 500 mg/kg. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011). Under the conditions of the study, resorcinol was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to 3-methoxy-5-cresol.

Based on the data available, 3,5-dimethoxytoluene and resorcinol do not present a concern for genotoxic potential, and this can be extended to 3-methoxy-5-cresol.

Additional References: Haworth et al., 1983; Hachiya and Takizawa, 1994; Jansson et al., 1988.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 3-methoxy-5-cresol or any read-across materials. The total systemic exposure to 3-methoxy-5-cresol 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 3-methoxy-5-cresol or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3-methoxy-5-cresol (0.18 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/25/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 3-methoxy-5-cresol or any read-across materials. The total systemic exposure to 3-methoxy-5-cresol 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 3-methoxy-5-cresol or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 3-methoxy-5-cresol (0.18 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/25/21.

11.1.4. Skin sensitization

Based on read-across material 2-methoxy-4-methylphenol (CAS # 93-51-6), 3-methoxy-5-cresol was assigned a NESIL of 110 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

11.1.4.1. Risk assessment. Limited data are available on the skin sensitization potential of 3-methoxy-5-cresol. Therefore, a structurally related material, 2-methoxy-4-methylphenol (CAS # 93-51-6; see Section VI), was used for the risk assessment of 3-methoxy-5-cresol. Based on the chemical structure, 3-methoxy-5-cresol is not predicted to react with skin proteins directly; however, read-across material 2-methoxy-4-methylphenol is predicted to react with skin proteins directly (Toxtree v3.1.0). Read-across material 2-methoxy-4-methylphenol was found to be negative in an *in chemico* direct peptide reactivity assay (DPRA) and the KeratinoSens, but positive in the h-CLAT and U-SENS tests (Urbisch, 2015; Natsch, 2013; Piroird et al., 2015). In a murine local lymph node assay (LLNA), read-across material 2-methoxy-4-methylphenol was found to be sensitizing with an EC3 value of 5.8% (1450 μg/cm^2) (Basketter et al., 2003; Kimber and Basketter, 1992). In a guinea pig open epicutaneous test (OET), 3-methoxy-5-cresol showed positive skin sensitization reactions (RIFM, 1975c). Additionally, in a guinea pig maximization test, read-across material 2-methoxy-4-methylphenol presented reactions indicative of sensitization (RIFM, 1990). In a Confirmation of No Induction in Humans test (CNIH) conducted at 0.5% (250 μg/cm^2) of 3-methoxy-5-cresol in dimethyl phthalate, no reactions indicative of sensitization were observed in any of the 53 volunteers (RIFM, 1996). Additionally, in a CNIH conducted at 0.1% (118 μg/cm^2) with read-across material, 2-methoxy-4-methylphenol in 3:1 ethanol: diethyl phthalate, no reactions indicative of sensitization was observed in any of the 106 volunteers (RIFM, 1998).

Based on the weight of evidence (WoE) from the available data and read-across to 2-methoxy-4-methylphenol, 3-methoxy-5-cresol was assigned a WoE NESIL of 110 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b).

Additional References: RIFM, 2017b; RIFM, 1975b.

Literature Search and Risk Assessment Completed On: 06/04/

21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, 3-methoxy-5-cresol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. The available UV/Vis spectra (OECD TG 101) for 3-methoxy-5-cresol indicate no absorbance between 290 and 700 nm. The molar absorption coefficient for wavelengths between 290 and 700 nm is below the benchmark (1000 L mol^{-1} • cm^{-1}) of concern for phototoxic effects (Henry et al., 2009). 3-Methoxy-5-cresol was not reported to result in phototoxic responses in guinea pigs; however, the report does not provide details on the concentration utilized during the study (RIFM, 1975a). Based on UV/Vis absorption spectra and study data, 3-methoxy-5-cresol would not be expected to present a concern for phototoxicity. Based on UV/Vis absorption spectra, 3-methoxy-5-cresol would not be expected to 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 in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/26/21.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 3-methoxy-5-cresol 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 3-methoxy-5-cresol. Based on the Creme RIFM Model, the inhalation exposure is 0.00083 mg/day. This exposure is 1687 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3-methoxy-5-cresol 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, 3-methoxy-5-cresol 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 3-methoxy-5-cresol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

Table 1
Data summary for 2-methoxy-4-methylphenol as read-across material for 3-methoxy-5-cresol.

LLNA Weighted Mean EC3 Value (No. Studies) μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
1450 [1]	Moderate	118	NA	NA	110

NOEL = No observed effect level; CNIH = Confirmation of no induction in humans 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 CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 3-methoxy-5-cresol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

Biodegradation:

RIFM, 2000a: Ready biodegradation of the test material was evaluated according to the OECD 301F method. Under the test conditions, the test material undergoes 89% biodegradation after 28 days.

Ecotoxicity:

No data available.

Other available data:

3-Methoxy-5-cresol has been pre-registered for REACH with no additional data.

11.2.4. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1688			1000000	1.688	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	0.9	0.9
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 further assessment is necessary.

The RIFM PNEC is 1.688 μg/L. The revised PEC/PNECs for EU and NA are not applicable; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 06/04/21.

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 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

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 12/13/21.

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. 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.2022.113314.

Appendix

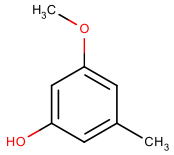
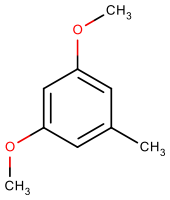
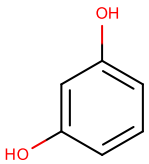
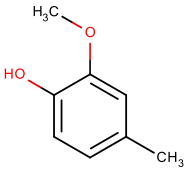
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). 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 Chemical 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 (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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13 (Patlewicz et al., 2008).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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	Read-across Material	Read-across Material
Principal Name	3-Methoxy-5-cresol	3,5-Dimethoxytoluene	Resorcinol	2-Methoxy-4-methylphenol
CAS No.	3209-13-0	4179-19-5	108-46-3	93-51-6
Structure				
Similarity (Tanimoto Score)		0.67	0.23	0.90
Endpoint		• Genotoxicity	• Genotoxicity	• Skin Sensitization
Molecular Formula		$C_9H_{12}O_2$	$C_6H_6O_2$	$C_8H_{10}O_2$
Molecular Weight (g/mol)	138.16	152.19	110.11	138.17
Melting Point (°C, EPI Suite)	40.45	12.07	109.80	5.50
Boiling Point (°C, EPI Suite)	230.36	244.00	280.00	221.00
Vapor Pressure (Pa at 25°C, EPI Suite)	3.19	5.00	0.07	7.92
Water Solubility (mg/L, at 25°C, WSKOW v1.42 in EPI Suite)	4810.00	365.50	717000.00	2093.00
Log K_{OW}	2.14	2.70	0.80	1.88
J_{max} (μg/cm^2/h, SAM)	174.65	20.99	6194.20	51.32
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	0.00	2.11	0.00	0.13
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	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)**	No alert found	1,3-dialkoxy-benzene	No alert found	
Oncologic Classification	Phenol-type Compounds	Not classified	Phenol-type Compounds	
Skin Sensitization				
Protein Binding (OASIS v1.1)	No alert found			No alert found
Protein Binding (OECD)	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)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found			No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified.			Alert for Michael Acceptor identified.
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on 3-methoxy-5-cresol (CAS # 3909-13-0). 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, 3,5-dimethoxytoluene (CAS # 4179-19-5), resorcinol (CAS # 108-46-3), and 2-methoxy-4-methylphenol (CAS # 93-51-6) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 3,5-Dimethoxytoluene (CAS # 4179-19-5) was used as a read-across analog for the target material, 3-methoxy-5-cresol (CAS # 3909-13-0), for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of m-methoxy toluene.
  - o The key difference between the target material and the read-across analog is that the target material has 3-hydroxy and 5-methoxy substitutions, while the read-across analog has 3-methoxy and 5-methoxy substitutions on the aromatic ring. This structural difference is toxicologically insignificant.
  - 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 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 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.
- Resorcinol (CAS # 108-46-3) was used as a read-across analog for the target material, 3-methoxy-5-cresol (CAS # 3909-13-0), for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of m-substituted phenols.
  - o The key difference between the target material and the read-across analog is that the target material has 3-methoxy and 5-methoxy substitutions, while the read-across analog has only 3-hydroxy substitution. This structural difference is toxicologically insignificant.
  - 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 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 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.
- 2-Methoxy-4-methylphenol (CAS # 93-51-6) was used as a read-across analog for the target material, 3-methoxy-5-cresol (CAS # 3909-13-0), for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of methoxy substituted phenols.
  - o The key difference between the target material and the read-across analog has o-methoxy substitution while the target material has m-Methoxy substitution. This structural difference is toxicologically insignificant.
  - 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 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 read-across analog has a skin sensitization reactivity domain alert as a Michael acceptor. This is due to the fact that the read-across analog has an *o*-methoxy substitution, which upon metabolism will form an *o*-hydroxy group. This yields a catechol structure, which is known to be reactive with skin proteins. The target has an *m*-methoxy substitution, which does not form a catechol structure on the target. This yields more reactivity to the read-across analog 2-methoxy-4-methylphenol, making this read-across analog a conservative selection.
  - 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.

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