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RIFM fragrance ingredient safety assessment, 2,6-dimethoxyphenol, CAS Registry Number 91-10-1

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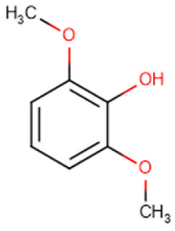
Name: 2,6-Dimethoxyphenol
CAS Registry Number: 91-10-1



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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 estimate of aggregate exposure to individuals across a population (Comiskey et al.,

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2015, 2017; Safford et al., 2015a; Safford et al., 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.

2,6-Dimethoxyphenol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog guaiacol (CAS # 90-05-1) show that 2,6-dimethoxyphenol is not expected to be genotoxic. Data on read-across analog catechol (CAS # 120-80-9) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for 2,6-dimethoxyphenol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 2,6-dimethoxyphenol 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, and the exposure to2,6-dimethoxyphenol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2,6-dimethoxyphenol 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.	(ECHA REACH Dossier: Guaiacol; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 3.3 mg/kg/day.	OECD (2003)
Reproductive Toxicity: NOAEL = 160 mg/kg/day.	(ECHA REACH Dossier: Pyrocatechol; ECHA, 2013)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	RIFM (2003)
Phototoxicity/Photoallergenicity: Not phototoxic/not expected to be photoallergenic.	(UV/Vis Spectra; RIFM, 2015)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.80 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 2.665 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 1141.5 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: 1141.5 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 1.141 μg/L

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

1. Identification

1. **Chemical Name:** 2,6-Dimethoxyphenol
2. **CAS Registry Number:** 91-10-1
3. **Synonyms:** 2-Hydroxy-1,3-dimethoxybenzene; Phenol, 2,6-dimethoxy-; Pyrogallol dimethyl ether; Syringol; 1,2,6-Dimethoxyphenol; 2,6-Dimethoxyphenol
4. **Molecular Formula:** $C_8H_{10}O_3$
5. **Molecular Weight:** 154.16 g/mol
6. **RIFM Number:** 6356
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 249.07 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (Fragrance Materials Association [FMA]), >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 1.15 (Smith et al., 2002), 1.11 (Smith et al., 2002), 1.16 (EPI Suite)
4. **Melting Point:** 55.14 °C (EPI Suite)
5. **Water Solubility:** 7578 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00166 mm Hg at 20 °C (EPI Suite v4.0), 0.002 mm Hg at 20 °C (FMA), 0.00307 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm under neutral and acidic conditions. Molar absorption coefficients under the biologically relevant neutral condition (0 L mol^{-1} • cm^{-1}) and acidic conditions (0 L mol^{-1} • cm^{-1}) are below the benchmark (1000 L mol^{-1} • cm^{-1}). The molar absorption coefficient under basic conditions (1905 L • mol^{-1} • cm^{-1}) is above the benchmark.
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1. <0.1 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:** 0.00020% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.000036 mg/kg/day or 0.0028 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.00027 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 et al., 2015; Safford et al., 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 et al., 2015; Safford et al., 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

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

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

2. Analogs Selected:
   a. **Genotoxicity:** Guaiacol (CAS # 90-05-1)
   b. **Repeated Dose Toxicity:** Catechol (CAS # 120-80-9)
   c. **Reproductive Toxicity:** Catechol (CAS # 120-80-9)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/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

2,6-Dimethoxyphenol is reported to occur in the following foods by the VCF*:

Coffee	Pear brandy
Fish	Pork
Grape brandy	Salami
Katsuobushi (dried bonito)	Shrimps (prawn)
Licorice (*Glycyrrhiza* species)	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

Available; accessed on 08/23/21 (ECHA, 2017).

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, 2,6-dimethoxyphenol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2,6-Dimethoxyphenol was found to be non-mutagenic in a bacterial reverse mutation assay equivalent or similar to OECD 471 using the plate incorporation method using 4 *S. typhimurium* strains, and 2 *E. coli* strains dosed up to 1.6 mg/plate (*S. typhimurium*) and 1000 μg/mL (*E. coli)* both with and without metabolic activation (Douglas et al., 1980; McMahon et al., 1979).

To further investigate the mutagenic activity of 2,6-dimethoxyphenol, read-across was made to guaiacol (CAS # 90-05-1; see Section VI).

The mutagenic activity of guaiacol has been evaluated in a bacterial reverse mutation assay conducted in an equivalent manner to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with guaiacol in dimethyl sulfoxide (DMSO) 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 (ECHA, 2011). Under the conditions of the study, guaiacol was not mutagenic in the Ames test, and this can be extended to 2, 6-dimethoxyphenol.

There are no studies assessing the clastogenic activity of 2,6-dimethoxyphenol; however, read-across can be made to guaiacol (CAS # 90-05-1; see Section VI).

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 body weight 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, 2011). 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 2,6-dimethoxyphenol.

Based on the data available, guaiacol does not present a concern for genotoxic potential, and this can be extended to 2,6-dimethoxyphenol.

Additional References: Nestmann et al., 1980; Nestmann and Lee, 1983; Florin et al., 1980; McMahon et al., 1979; Ohshima et al., 1989; Aeschbacher et al., 1989; Ferretti et al., 1977; Florin et al., 1980; Rapson et al., 1980; Douglas et al., 1980; Haworth et al., 1983; Jansson et al., 1986; Stich et al., 1981; Tsutsui et al., 1987; Ohshima et al., 1989; Rosin (1984); Someya et al., 2008; Miyachi and Tsutsui, 2005; Hamaguchi and Tsutsui, 2000; Hikiba et al., 2005.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.2. Repeated dose toxicity

The MOE for 2,6-dimethoxyphenol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. The repeated dose data on 2,6-dimethoxyphenol are insufficient for the repeated dose endpoint. A dietary 90-day subchronic toxicity study conducted in rats determined the NOAEL to be 5.99 and 6.58 mg/kg/day in males and females, respectively, the only dosage tested (Posternak et al., 1969).

Read-across material catechol (CAS # 120-80-9; see Section VI) has sufficient data that can be used to support the repeated dose toxicity endpoint. An OECD 422/GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Wistar rats. Groups of 10 rats/sex/dose were exposed to the test material, catechol, at doses of 30, 80, or 160 mg/kg/day via oral gavage in water once daily, 7 days per week. Males were treated for a minimum of 4 weeks and females for approximately 7 weeks (prior to mating for 2 weeks, through the pairing and gestation periods, until the F1 generation reached day 4 postpartum). Mortality was observed at 160 mg/kg/day; during the pre-pairing period, 1 male and 1 female were found dead on days 3 and 14, respectively, and during the mating period, 1 male was found dead on day 10. Body weight and bodyweight gains were not affected by the treatment for males and females. In males, the level of total bilirubin was statistically significantly increased in the high-dose group as compared to the control. At the high dose, liver weights were statistically significantly increased in males and females. This was considered to be of metabolic nature since only hepatocellular hypertrophy and no liver injury was observed during the histopathological examination. In addition, a statistically significant increase in the absolute weight of kidneys was also observed in males and females. In males, this was caused by the slightly increased severity of hyaline droplets, which were considered to be an incidental increase of a spontaneous lesion. The relative kidney weights for males and females were comparable to the control group. At the high dose, diffuse hepatocellular hypertrophy was recorded at minimal severity in 3 males and 2 females. This was correlated with the significantly increased absolute weight of the liver, as well as with macroscopical findings consisting of enlargement. However, there were no further indicators of liver injury; hence, this lesion was considered to be metabolic and adaptive in nature. In mid- and high-dose groups, the incidence and severity of squamous hyperplasia in the stomach were increased in both males and females. Thus, the NOAEL for repeated dose toxicity was considered to be 30 mg/kg/day, based on the squamous hyperplasia in the stomach (ECHA, 2013).

In addition, there are carcinogenicity studies available for catechol. Group of 30 male F344 rats were fed catechol at 0%, 0.1%, 0.2%, 0.4%, and 0.8% (equivalent to 33, 65, 141, and 318 mg/kg/day) for up to 104 weeks. Five rats in each group were euthanized at 34 weeks, and the remaining were euthanized at the end of the treatment period. There were no clinical abnormalities or mortalities related to catechol observed during the treatment. Bodyweight gain was delayed (15%) for the male rats only in the high-dose group. Slight thickening of the pyloric region was observed at 0.4% and 0.8% at week 34. At the end of the study, marked to moderate thickening was also found in rats fed 0.2% of test material and above. Statistically significant adenomas and submucosal hyperplasias of the pyloric glands were developed in rats fed with 0.4% and 0.8% catechol by 34 weeks. Further significant adenomas were developed in rats fed with 0.2% catechol and above by 104 weeks, and significant submucosal hyperplasias were developed in rats at all dose groups. The NOAEL was considered to be 0.1% (33 mg/kg/day) at 34 weeks, and a LOAEL of 0.1% (33 mg/kg/day) was considered at 104 weeks. For 2 year study a NOAEL of 3.3 mg/kg/day was derived by dividing the LOAEL by 10 (33/10 = 3.3 mg/kg/day) (OECD, 2003; Hagiwara et al., 2001).

Therefore, the 2,6-dimethoxyphenol MOE for the reproductive toxicity endpoint can be calculated by dividing the catechol NOAEL in mg/kg/day by the total systemic exposure to 2,6-dimethoxyphenol, 3.3/0.00027, or 12222.

In addition, the total systemic exposure to 2,6-dimethoxyphenol (0.27 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: 10/15/21.

11.1.3. Reproductive toxicity

The MOE for2,6-dimethoxyphenol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2,6-dimethoxyphenol. Read-across material catechol (CAS # 120-80-9; see Section VI) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. An OECD 422/GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Wistar rats. Groups of 10 rats/sex/dose were exposed to the test material, catechol, at doses of 30, 80, or 160 mg/kg/day via oral gavage in water once daily, 7 days per week. Males were treated for a minimum of 4 weeks and females for approximately 7 weeks (prior to mating for 2 weeks, through the pairing and gestation periods until the F1 generation reached day 4 postpartum). Mortality was observed at 160 mg/kg/day; during the pre-pairing period, 1 male and 1 female were found dead on days 3 and 14, respectively, and during the mating period, 1 male was found dead on day 10. No treatment-related effects were seen with respect to reproductive parameters in males and females. Mean precoital time, conception rate, and fertility and gestation indices were not affected by the treatment. In addition, implantation rate and post-implantation loss were also not affected by the treatment. In the F1 generation, the mean number of pups at birth and on day 4 postpartum was not affected by the treatment at any dose groups. No treatment-related effects were seen in the sex ratio and weight development. At necropsy of pups, no treatment-related findings were noted. Thus, the NOAEL for developmental toxicity and fertility was considered to be 160 mg/kg/day, the highest dose tested (ECHA, 2013).

Therefore, the 2,6-dimethoxyphenol MOE for the developmental toxicity and fertility endpoint can be calculated by dividing the catechol NOAEL in mg/kg/day by the total systemic exposure to 2,6-dimethoxyphenol, 160/0.00027, or 592593.

In addition, the total systemic exposure to 2,6-dimethoxyphenol (0.27 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: 10/15/21.

11.1.4. Skin sensitization

Based on the existing data, 2,6-dimethoxyphenol presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, 2,6-dimethoxyphenol is not considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0). In a murine local lymph node assay (LLNA), 2,6-dimethoxyphenol was not found to be sensitizing up to 40% in 4:1 acetone:olive oil (AOO) (RIFM, 2003).

Based on the weight of evidence (WoE) from structural analysis and animal study, 2,6-dimethoxyphenol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/08/21.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorbance and *in vitro* study data, 2,6-dimethoxyphenol does not present a concern for phototoxicity. Based on UV/Vis absorbance, 2,6-dimethoxyphenol 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 the biologically relevant neutral condition, as well as acidic conditions; the corresponding molar absorption coefficients are below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Absorbance was observed under basic conditions, and the molar absorption coefficient was above the benchmark. However, basic conditions for the assay are defined as pH $>$ 10 and may not be biologically relevant for our purposes, where the route of exposure is topical. Furthermore, per the ICH S10 guidance on Photosafety Evaluation of Pharmaceuticals, some chromophores, including those with phenolic structures, are considered pH sensitive. In an *in vitro* 3T3 Neutral Red uptake assay,2,6-dimethoxyphenol was not predicted to be phototoxic based on mean photo-effect (RIFM, 2015). Based on the lack of absorbance under biologically relevant neutral pH and *in vitro* study data, 2,6-dimethoxyphenol does not present a concern for phototoxicity. Based on the lack of absorbance under biologically relevant neutral pH, 2,6-dimethoxyphenol 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 in the range of 290–700 nm under neutral and acidic conditions. The molar absorption coefficients under neutral and acidic conditions (0 L mol^{-1} • cm^{-1}) are below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009). Absorbance under the basic condition was greater, and the corresponding molar absorption coefficient (1905 L • mol^{-1} • cm^{-1}) was above the benchmark of concern. However, basic conditions for the assay are defined as a pH of 10 or greater and thus do not represent a biologically relevant condition.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2,6-Dimethoxyphenol 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 2,6-dimethoxyphenol. Based on the Creme RIFM Model, the inhalation exposure is 0.0028 mg/day. This exposure is 500 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: 10/15/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,6-dimethoxyphenol 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, 2,6-dimethoxyphenol 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 2,6-dimethoxyphenol 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, 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 2,6-dimethoxyphenol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

2,6-Dimethoxyphenol has been registered for REACH with no additional data available at this time.

11.2.5. 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	1.15	1.15

(*continued on next page*)

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1141			1000000	1.14	

(*continued*)

Exposure	Europe (EU)	North America (NA)
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

The RIFM PNEC is 1.141 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: 09/29/21.

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 02/25/22.

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.2022.113092.

Appendix

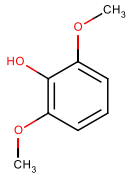
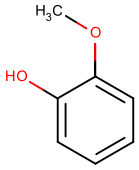
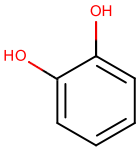
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 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 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.
- 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
Principal Name	2,6-Dimethoxyphenol	Guaiacol	Catechol
CAS No.	91-10-1	90-05-1	120-80-9
Structure			
Similarity (Tanimoto Score)		0.59	0.29
Endpoint		• Genotoxicity	• Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_8H_{10}O_3$	$C_7H_8O_2$	$C_6H_{10}O_2$
Molecular Weight (g/mol)	154.16	124.14	110.11
Melting Point (°C, EPI Suite)	56.50	32.00	105.00
Boiling Point (°C, EPI Suite)	261.00	205.00	245.50
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.41	13.73	0.49
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	17200.00	18700.00	461000.00
Log K_{OW}	1.15	1.32	0.88
J_{max} (μg/cm^2/h, SAM)	83.76	266.39	4556.38
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.02	0.12	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)	1,3-dialkoxy-benzene|H-acceptor-path3-H-acceptor	H-acceptor-path3-H-acceptor	
Oncologic Classification	Phenol-type Compounds	Phenol-type Compounds	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Methoxamine (Renal toxicity) Alert		Methyldopa (Hepatotoxicity) Alert|Methyldopa (Renal toxicity) Alert|Phenols (Mucous membrane irritation) Rank C|Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, impaired OH or NH_2 group		Weak binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (low reliability)		Non-toxicant (good 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	See Supplemental Data 3

Summary

There are insufficient toxicity data on 2,6-dimethoxyphenol (CAS # 91-10-1). 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 catechol (CAS # 120-80-9) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Guaiacol (CAS # 90-05-1) was used as a read-across analog for the target material, 2,6-dimethoxyphenol (CAS # 91-10-1), for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of phenols.
  - o The key difference between the target material and the read-across analog is that the target material has 2 ortho methoxy substituents, whereas the read-across analog has only one ortho methoxy substituent. 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 predicted to show DNA binding via P450 Michael addition upon metabolic transformation to a quinone. The data described in the genotoxicity section confirm that the read-across analog does not pose a concern for genotoxicity. Therefore, the data supersedes the prediction.
  - 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.
- Catechol (CAS # 120-80-9) was used as a read-across analog for the target material, 2,6-dimethoxyphenol (CAS # 91-10-1), for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog belong to a class of phenols.
  - o The key difference between the target material and the read-across analog is that the read-across analog has a hydroxyl group at the ortho position, whereas the target material has 2 ortho methoxy substituents. This structural difference makes the read-across more reactive than the target material.
  - 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 is predicted to be a toxicant by the CAESAR model for developmental toxicity. The read-across analog does not have any alert. The MOE for 2,6-dimethoxyphenol is adequate for the reproductive toxicity endpoint at the current level of use. The predictions are superseded by the data.
  - o Both the target material and the read-across analog present a renal toxicity alert for the repeated dose (HESS) classification scheme. The data described in the repeated dose toxicity section show that the MOE is adequate at the current level of use. The predictions are 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.

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