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Short review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT p-Methylanisole, CAS Registry Number 104-93-8

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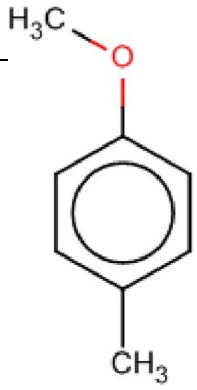
CAS Registry Number: 104-93-8



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
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
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 - Ultra Violet/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 under the limits described in this safety assessment.

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

Each endpoint discussed in this safety assessment 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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative 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 guidance relevant to human health and environmental protection.

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

p-Methylanisole was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that p-methylanisole is not genotoxic nor does it present a safety concern for skin sensitization under the current, declared levels of use. Data provided a calculated MOE > 100 for the repeated dose, developmental and reproductive toxicity endpoints. The local respiratory toxicity endpoint was completed using the TTC for a Cramer Class III material, and the exposure to p-methylanisole was below the TTC (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; p-methylanisole is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, p-methylanisole was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 1984; ECHA REACH Dossier: p-methylanisole)
Repeated Dose Toxicity: NOAEL = 33 mg/kg/day. (RIFM, 2013b)
Developmental and Reproductive Toxicity: NOAEL = 100 mg/kg/day and 570 mg/kg/day, respectively.
(RIFM, 2010a; RIFM, 2010b)
Skin Sensitization: Not a concern for skin sensitization. (Klecak, 1985; Klecak, 1979; ECHA REACH Dossier: 4-methylanisole)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 79% (OECD 301F) (RIFM, 2013a)
Bioaccumulation: Screening-Level: 26.4 L/Kg (US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48-h Algae EC50: 15.77 mg/L (US EPA, 2012a)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 48-hr Algae EC50: 15.77 mg/L (US EPA, 2012a)

RIFM PNEC is: 1.577 μg/L

• **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe < 1

1. Identification

1. **Chemical Name:** p-Methylanisole
2. **CAS Registry Number:** 104-93-8
3. **Synonyms:** Benzene, 1-methoxy-4-methyl-; p-Cresyl methyl ether; 4-Methoxytoluene; p-Methoxytoluene; Methyl p-cresyl ether; Methyl p-cresol; 4-Methyl-1-methoxybenzene; 4-Methylphenol methyl ether; ｱﾙｷﾙ(C = 1 ~ 3)ﾌｪﾆﾙｱﾙｷﾙ(C = 1 ~ 5)ｴｰﾃﾙ; 1-Methoxy-4-methylbenzene; Cresyl methyl ether para; p-Methylanisole
4. **Molecular Formula:** $C_8H_{10}O$
5. **Molecular Weight:** 122.17
6. **RIFM Number:** 239

2. Physical data

1. **Boiling Point:** 176 °C [FMA database], (calculated) 170.8 °C [US EPA, 2012a]
2. **Flash Point:** 151 °F [IFF Specification Sheet, 1989], 140 °F; CC [FMA database]
3. **Log K_{ow}:** 2.62 [US EPA, 2012a]
4. **Melting Point:** −23 °C [US EPA, 2012a]
5. **Water Solubility:** 527.1 mg/L [US EPA, 2012a]
6. **Specific Gravity:** .9689 [EOA, 1973 Sample 72–193], 0.968–0.972 [FMA database], 0.966–0.970 [FMA database]
7. **Vapor Pressure:** 1.3 mm Hg 20 °C [FMA database], 0.839 mm Hg @ 20 °C [US EPA, 2012a], 1.2 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A clear, colorless to very pale, yellow liquid with pungent, sweet odor suggestive of Ylang.

3. Exposure

1. **Volume of Use (Worldwide Band):** 100–1000 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.024% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.000083 mg/kg/day or 0.0061 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.00046 mg/kg/day (RIFM, 2014)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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, 2017; Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** 58%

RIFM, 1993: An *in vivo* excretion and tissue distribution study was conducted with radioactive p-methylanisole after topical application in rats. Groups of 4 male Sprague-Dawley CD rats were administered topical doses of [14C]p-methylanisole formulated in diethyl phthalate. Each group was administered separate doses at nominal levels of 100, 320 and ca. 1000 mg/kg body weight. The dose was applied over an area of 16 cm^2. The treated area was occluded for 6 h after dose application. At this time, the dose dressing and residual dose were removed using cotton wool swabs moistened with diethyl phthalate. Urine, feces and expired air were collected for 72 h after dose application. At this time, rats were euthanized, and whole blood and tissues (liver, kidney, GIT, fat and treated skin) were taken for radioactivity measurement. After topical application to groups of 4 rats, the total urinary excretion accounted for about 12% of the dose in rats dosed at 100 and 320 mg/kg and about 20% of the dose in rats dosed at 1000 mg/kg. The total excretion of radioactivity in feces accounted for 0.05–0.17% of the dose. Radioactivity present in expired air traps accounted for about 11, 23 and 37% of the dose at dose levels of 100, 320 and 1000 mg/kg, respectively. After 6 h of exposure, approximately 74, 59 and 36% of the dose was recovered in washings of the treated skin in rats dosed at 100, 320 and 1000 mg/kg, respectively. At 72 h after dosing, 0.02–0.05% of the dose was in the treated skin taken from these rats after being euthanized. Radioactivity recovered from each group of rats accounted for a mean of approximately 94–97% of the [14C]p-methylanisole administered. There was a dose-dependent increase in % skin absorption (from ~23, 35 and 58%, respectively). At the highest dose, a conservative total absorbed dose (urine, feces, expired air, carcass, tissues, blood, and treated skin) was determined to be ~58%.

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High

Expert Judgment	Toxtree 2.6	OECD QSAR Toolbox 3.1
III	III	III

2. Analogs Selected:
   a. Genotoxicity: None
   b. Repeated Dose Toxicity: None
   c. Developmental and Reproductive Toxicity: None
   d. Skin Sensitization: None
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: None
   g. Environmental Toxicity: None
3. Read across justification: None

6. Metabolism

No relevant data available for inclusion in this safety assessment.

7. NaturaL occurrence (discrete chemical) or composition (NCS)

p-Methylanisole is reported to occur in the following foods* and in some natural complex substances (NCS):

Blue Cheeses
Buckwheat
Cheese, various types
Rooibos tea (Aspalathus linearis)
Starfruit (Averrhoa carambola L.)
Tapereba, caja fruit (*Spondias lutea* L.)

Tomato (Lycopersicon esulentum Mill.)
Vanilla

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

8. IFRA standard

None.

9. REACH dossier

Two available, accessed on 10/20/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on current existing data, p-methylanisole does not present a concern for genotoxicity.

10.1.2. Risk assessment

The mutagenic activity of p-methylanisole has been evaluated in a bacterial reverse mutation assay conducted using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were treated with p-methylanisole in dimethyl sulfoxide (DMSO) at concentrations up to 50 μL/plate. No increases in the mean number of revertant colonies were observed at any dose tested in the presence or absence of S9 (RIFM, 1984). Under the conditions of the study, p-methylanisole was not mutagenic in the Ames test.

The clastogenic activity of p-methylanisole 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 500, 1000 or 2000 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h; the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA REACH Dossier: p-methylanisole). Under the conditions of the study, p-methylanisole was not considered to be clastogenic in the *in vivo* micronucleus test.

Based on the data available, p-methylanisole does not present a concern for genotoxicity.

Additional References: RIFM, 1980; Florin et al., 1980; RIFM, 1988; ECHA REACH Dossier: p-methylanisole; Heck et al., 1989; RIFM, 1989a; RIFM, 1989b.

Literature Search and Risk Assessment Completed on: 03/16/2017.

10.1.3. Repeated dose toxicity

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

10.1.4. Risk assessment

There are sufficient repeated dose toxicity data on p-methylanisole for the repeated dose toxicity endpoint. An OECD/GLP 407 gavage 28-day subchronic toxicity study was conducted in Wistar rats. Groups of 5 rats/sex/dose were administered via gavage test material, p-methylanisole at doses of 0, 100, 300 or 1000 mg/kg/day in olive oil 5 days/week for 4 weeks. At 1000 mg/kg/day, treatment-related effects included clinical signs (salivation, ataxia, and tremor, labored respiration), increased cholesterol (females), increased liver weights accompanied by diffuse hypertrophy of the hepatocytes and single cell necrosis of hepatocytes. Decreased spleen and thymus weights in males and increased kidney weights in females were not accompanied by histopathological changes. At 300 mg/kg/day, treatment-related effects included salivation and decreased spleen weights in the males, which were not accompanied by histopathological changes. Clinical symptoms of salivation, ataxia, and tremor were observed only after the administration of the test material, most probably a result of the irritating potential of the test material not related to systemic toxicity. Hyperkeratosis and focal hyperplasia was observed in the forestomach of one male in the highest dose group. Thus, the NOAEL for repeated dose toxicity was considered to be 100 mg/kg/day, based on organ weight changes in the higher dose groups (RIFM, 2013b).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 study. The safety factor has been approved by The Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 100/3 or 33 mg/kg/day.

Therefore, the p-methylanisole MOE for the repeated dose toxicity endpoint can be calculated by dividing the p-methylanisole NOAEL in mg/kg/day by the total systemic exposure to p-methylanisole, 33/0.00046 or 71739.

In addition, the total systemic exposure to p-methylanisole (0.46 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

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

Additional References: Brunsborg et al., 1994.

Literature Search and Risk Assessment Completed on: 03/20/2017.

10.1.5. Developmental and reproductive toxicity

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

10.1.6. Risk assessment

There are sufficient developmental toxicity data on p-methylanisole for the developmental toxicity endpoint. An OECD/GLP 421 study conducted in rats were administered via both the oral and dermal routes with test material, p-methylanisole at doses of 0, 100, 300 or 1000 mg/kg/day. After oral gavage exposure, the NOAEL for developmental toxicity was determined to be 100 mg/kg/day, based on reduced pup weights and pre- and post-natal offspring mortality (RIFM, 2010b). The post-natal effects were at least partially secondary to disturbed maternal care. After dermal exposure, the NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, the highest dosage tested (RIFM, 2010a). A developmental toxicity study was conducted on p-methylanisole using generational and juvenile exposure protocols with and without direct pup exposure during lactation using p-methylanisole as test compound. The parental (F0) animals were mated at a ratio of 2:1, male:females. The F0 animals were gavaged with test material at doses of 0, 8, 16, 32, 64, 125 or 250 mg/kg/day. The animals were divided into 4 different cohorts. In cohort 1, the females were dosed 2 weeks pre-mating, during mating, gestation and lactation and pups received a vehicle from post-natal day (PND) 10–21. The pups were then individually dosed with test material from PND21 to PND50. In cohort 2, the females were treated with test material 2 weeks pre-mating to lactation day (LD) 10. The pups were then directly

exposed from PND10 to PND50. In cohort 3, the F0 females were not dosed with the test material. The pups were directly dosed with test material from PND10 to PND50. In cohort 4, the F0 females were not dosed with the test material. The pups were dosed directly from PND21 to PND50. No adverse effects were reported in the F0 females. The fertility and reproductive performance were affected, and the litter size was reduced at the highest dose level only. Relative liver and kidney weights were increased in the F1 animals of the highest dose group. Hormone levels (T4) were affected. Platelet and eosinophil counts were decreased at the highest dose level only. Absolute and relative spleen weights were decreased in the highest dose level animals only. Apart from TNF-alpha and interleukin-13 plasma levels, no other alterations in functional immune parameters were related to treatment with p-methylanisole (Tonk et al., 2015). The Expert Panel for Fragrance Safety* reviewed the report and agreed that there was no clear dose response, and the number of animals studied were not reported; the study was not considered to be suitable for the safety assessment. The most conservative NOAEL of 100 mg/kg/day from the OECD 421 gavage study was considered for the developmental toxicity endpoint. **Therefore, the p-methylanisole MOE for the developmental toxicity endpoint can be calculated by dividing the p-methylanisole NOAEL in mg/kg/day by the total systemic exposure to p-methylanisole, 100/0.00046 or 217391.**

There are sufficient reproductive toxicity data on p-methylanisole for the reproductive toxicity endpoint. An OECD/GLP 421 developmental and reproductive toxicity screening test was conducted in rats with test material, p-methylanisole via both the oral and dermal routes at doses of 0, 100, 300 or 1000 mg/kg/day. After oral gavage exposure, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2010b). After dermal exposure, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dosage tested (RIFM, 2010a). Since the dermal route is more relevant to human exposure to fragrances, the NOAEL from the OECD 421 study via dermal exposure was selected for this safety assessment. To account for bioavailability following dermal application, data from an excretion and tissue distribution study conducted in rats following topical administration (RIFM, 1993; see Section 4) were used to revise the NOAEL of 1000 mg/kg/day to reflect the systemic dose. At a dermal penetration of 57% of the applied dose, the revised reproductive toxicity NOAEL from the dermal study was 570 mg/kg/day. **Therefore, the p-methylanisole MOE for the reproductive toxicity endpoint can be calculated by dividing the p-methylanisole NOAEL in mg/kg/day by the total systemic exposure to p-methylanisole, 570/0.00046 or 1239130.**

In addition, the total systemic exposure to p-methylanisole (0.46 µg/kg/day) is below the TTC (1.5 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/21/2017.

10.1.7. Skin sensitization

Based on existing data, p-methylanisole does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on existing data, p-methylanisole does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), p-methylanisole was found to be non-sensitizing up to 50% (ECHA REACH Dossier: 4-methylanisole). In a guinea pig open epicutaneous test, p-methylanisole did not present reactions indicative of sensitization (Klecak, 1979, 1985). In a human maximization test, no skin sensitization reactions were observed when 2% or 1380 µg/cm^2 p-methylanisole in petrolatum was used for induction and challenge (RIFM, 1971). Based on the weight of evidence from structural analysis, animal and human studies, p-methylanisole does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/23/2017.

10.2. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, p-methylanisole would not be expected to present a concern for phototoxicity or photoallergenicity.

10.3. Risk assessment

There are no phototoxicity studies available for p-methylanisole in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} · cm^{-1} (Henry et al, 2009). Based on the lack of significant absorbance in the critical range, p-methylanisole does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/28/2017.

10.3.1. Local Respiratory Toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The material, p-methylanisole, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

10.3.2. Risk assessment

There are no inhalation data available on p-methylanisole. Based on the Creme RIFM model, the inhalation exposure is 0.0061 mg/day. This exposure is 77.0 times lower than the Cramer Class III TTC value of 0.47 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: 03/21/2017.

10.4. Environmental endpoint summary

10.4.1. Screening-level assessment

A screening-level risk assessment of p-methylanisole was performed following the RIFM Environmental Framework (Salvito et al., 2002) that provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (US EPA, 2012b; providing chemical class specific ecotoxicity estimates) is used, and a lower uncertainty factor is applied. Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the

actual tonnage and not the extremes noted for the range. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Following the RIFM Environmental Framework, p-methylanisole was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify p-methylanisole as persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.4.2. Risk assessment

Based on the current Volume of Use (2011), p-methylanisole presents a risk to the aquatic compartment in the screening-level assessment.

10.4.3. Key studies

10.4.3.1. Biodegradation. RIFM, 2013a: The ready biodegradability of p-methylanisole was determined by the Manometric Respirometry Test according to OECD 301F guidelines. 30 mg/L of the test material undergoes 79% biodegradation after 28 days in the test conditions.

10.4.3.2. Ecotoxicity. No data available.

Other available data:

p-Methylanisole has been registered under REACH and the following data is available:

A 96-h fish *Leuciscus idus* (Golden orfe) acute toxicity study was conducted following the DIN 38412 L15 and the LC50 was reported to be 68.2 mg/L.

A *Daphnia magna* acute study was conducted according to the OECD 202 guidelines. The 48-h EC50 was reported to be 27 mg/L.

An algae acute study was reported according to the DIN 38412 method. The 72-h EC50 was reported to be > 500 mg/L.

10.4.4. Risk assessment refinement

Since p-methylanisole has passed the screening criteria, REACH data is reported only for completeness and has not been used for PNEC calculations.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	<u>47.59 mg/L</u>			1,000,000	0.04759 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	27.75 mg/L	16.70 mg/L	<u>15.77mg/L</u>	10,000	1.577 µg/L	Neutral organics

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

Exposure	Europe	North America
Log K_{ow} Used	2.62	2.62
1Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 1.577 µg/L. The revised PEC/PNECs for EU and NA < 1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 03/20/2017.

11. Literature Search*

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

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

This is not an exhaustive list.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2018.01.041.

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