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RIFM fragrance ingredient safety assessment, *p*-cresol, CAS Registry Number 106-44-5

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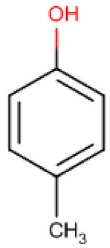

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. Proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe-use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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
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, 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,

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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.

p-Cresol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *p*-cresol is not genotoxic. Data on *p*-cresol provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The No Observed Adverse Effect Level (NOAEL) for skin depigmentation is 0.05% (Maximum Safe-Use Level: 0.005%). The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/violet (UV/Vis) spectra; *p*-cresol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material; exposure to *p*-cresol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; *p*-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.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: p-Cresol; ECHA, 2011; NTP, 1992)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day.	(ECHA REACH Dossier: p-Cresol; ECHA, 2011)
Developmental and Reproductive Toxicity: Developmental NOAEL = 100 mg/kg/day. Fertility NOAEL = 175 mg/kg/day.	EPA, (1988a)
Skin Depigmentation: NOAEL = 0.05%; Maximum Safe-Use Level: 0.005%	(ECHA REACH Dossier: p-Cresol; ECHA, 2011)
Skin Sensitization: No safety concerns at current, declared use levels. Exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/not photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1982)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value:100% (OECD 302B)	(ECHA REACH Dossier: p-Cresol; ECHA, 2011)
Bioaccumulation: Screening-level: 8.85 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 129.4 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: 129.4 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.1294 μg/L

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

1. Identification

1. **Chemical Name:** *p*-Cresol
2. **CAS Registry Number:** 106-44-5
3. **Synonyms:** 4-Cresol; *p*-Cresylic acid; 1-Hydroxy-4-methylbenzene; *p*-Hydroxytoluene; 1-Methyl-4-hydroxybenzene; *p*-Methylphenol; Phenol, 4-methyl-; 4-Methylphenol; ｸﾚｿﾞｰﾙ; para-Cresol; *p*-Cresol
4. **Molecular Formula:** C_7H_8O
5. **Molecular Weight:** 108.14
6. **RIFM Number:** 353
7. **Stereochemistry:** One possible stereoisomer

2. Physical data

1. **Boiling Point:** 202 °C (Fragrance Materials Association [FMA]), 190.8 °C (EPI Suite)
2. **Flash Point:** 86 °C (Globally Harmonized System), 187 °F; CC (FMA)
3. **Log K_{OW}:** 1.97 (Abraham, 1995), 1.94 (Smith, 2002), 1.97 (Smith, 2002), 1.94 (Patel, 2002), Log Pow = 2.0 (Ohlenbusch, 2001), 2.06 (Huang, 2003), 2.06 (EPI Suite)
4. **Melting Point**: 32 °C (FMA), 15.69 °C (EPI Suite)
5. **Water Solubility:** 9246 mg/L (EPI Suite)
6. **Specific Gravity:** 1.034 (FMA)
7. **Vapor Pressure:** 0.073 mm Hg at 20 °C (EPI Suite v4.0), 0.07 mm Hg at 20 °C (FMA), 0.124 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** White crystals with a phenolic odor

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0.3)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0030% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000023 mg/kg/day or 0.0018 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00016 mg/kg/day (RIFM, 2019)

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

5. Derivation of systemic absorption

1. **Dermal:** 100%

Hinz (1991): An *in vitro* dermal absorption study was conducted in mice using flow-through diffusion cells. Radiolabeled *p*-cresol (4 μg/cm^2) in acetone was applied to full-thickness hairless mouse skin. The donor chamber was not occluded. The receptor chamber of the diffusion cell was kept at a constant temperature and perfused with normal saline. Samples of the receptor phase were collected up to 48 h post-dose and analyzed using liquid scintillation counting. The maximum flux was 25% of the dose per hour with a Tmax of 2 h. The log mean maximum skin penetration rate was 1.391. The 24-h cumulative absorption was 77 ± 3% of the applied dose.

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:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None

Read-across Justification: None.

7. Metabolism

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

8. Natural occurrence

p-Cresol is reported to occur in the following foods by the VCF*:
Asparagus (*Asparagus officinalis* L.)
Beef.
Beer.
Black currants (*Ribes nigrum* L.)
Buckwheat.
*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

Available; accessed 02/28/20 (ECHA, 2011)

10. Conclusion

The maximum acceptable concentrations[a] in finished products for *p*-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)	0.0050
2	Products applied to the axillae	0.0050
3	Products applied to the face/body using fingertips	0.0050
4	Products related to fine fragrances	0.0050
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.0050

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.0050
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.0050
5D	Baby cream, oil, talc	0.0017
6	Products with oral and lip exposure	0.0050
7	Products applied to the hair with some hand contact	0.0050
8	Products with significant ano-genital exposure (tampon)	0.0017
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.0050
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.0050
10B	Aerosol air freshener	0.0050
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0017
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For *p*-cresol, the basis was the reference dose of 0.50 mg/kg/day, a predicted skin absorption value of 80%, and a skin depigmentation NOAEL of 0.05% (Maximum Safe-Use Level: 0.005%).

[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 v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of *p*-cresol has been evaluated in a bacterial reverse mutation assay conducted in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with *p*-cresol in dimethyl sulfoxide (DMSO) at concentrations up to/of 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, *p*-cresol was not mutagenic in the Ames test.

The clastogenicity of *p*-cresol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovary cells were treated with *p*-cresol in DMSO at concentrations up to 3010 μg/mL in the presence and absence of metabolic activation. Statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with and without S9 metabolic activation (ECHA, 2011). Under the conditions of the study, *p*-cresol was considered to be clastogenic in the *in vitro* chromosome aberration assay.

The clastogenic activity of *p*-cresol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in an equivalent manner to OECD TG 474. The test material was administered in feed via oral administration to groups of male and female B6C3F1 mice. Doses of 0, 625, 1250, 2500, 5000, and 10000 ppm were administered. Mice from each dose level were euthanized at 13 weeks, and the bone marrow was extracted and examined for normochromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated normochromatic erythrocytes in the bone marrow (NTP, 1992). Under the conditions of the study, *p*-cresol was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, *p*-cresol does not present a concern for genotoxic potential.

Additional References: NTP, 2008; Florin (1980); Nestmann (1980); Pool (1982); Douglas (1980); Jansson (1986); Cheng (1984); Ohshima (1989); Massey (1994); Levan (1948); Wong (1999); Kubo (2002); EPA, 1988b; EPA, 1989a.

Literature Search and Risk Assessment Completed On: 04/17/20.

11.1.2. Repeated dose toxicity

The MOE following oral exposure for *p*-cresol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. Toxicity data on *p*-cresol have been extensively reviewed by several organizations, among which Health Canada provides the most recent review (Health Canada, 2016). Repeated dose toxicity for *p*-cresol or *m*-/*p*-cresol (cresol) has been studied in rats and mice following dietary or gavage administration over subchronic (28 days) as well as chronic (2-years) durations. The major findings reported are lesions in the nasal cavity and respiratory tract attributed to inhalation of *p*-cresol from the diet. Such findings have been reported from studies on *p*-cresol or mixed cresols from short- or long-term exposures. It was concluded that respiratory tract lesions reported in studies with *p*-cresol or mixed cresols were due to local effects resulting from inhalation of *p*-cresol from the diet and not as a result of systemic toxicity. Although the NTP presents equivocal evidence for carcinogenicity due to *p*-cresol exposure, the ECHA Co-RAP evaluation suggests that the available data do not present a carcinogenic hazard to humans (NTP, 2008; ECHA, 2016).

From all the available studies on *p*-cresol, the most conservative NOAEL was available from the 90-day gavage OECD 408 study. The study was conducted with *p*-cresol administered to groups of 30 Sprague Dawley rats/sex/dose at doses of 0 (corn oil), 50, 175, or 600 mg/kg/day. Mortality was reported among females (3/30) in the high-dose group. Clinical signs among animals that died included tremors, convulsions, and coma prior to death. Additionally, other clinical signs reported among treated animals included lethargy, excessive salivation, tremors, convulsions, and coma. Body weight and bodyweight gains were significantly reduced among high-dose group animals. Relative kidney weights were increased among mid- and high-dose group males. High-dose group males showed an increase in relative testes weights. Relative kidney weights increased in high-dose group animals. Hematological alterations reported among mid-dose females included reductions in RBC count, hemoglobin concentration, and hematocrit. However, other correlating physiological responses to the mild anemic state (reticulocytes, macrocytosis, elevated numbers of RBC) were not evident. Altered clinical chemistry parameters comprised of statistically significant elevations in ALT (at interim and terminal sacrifices) and AST in high-dose females were attributed to unusually high values in 4 animals. Serum cholesterol was statistically significantly increased in high-dose females (terminal sacrifice only), whereas total protein was increased in mid- and high-dose males. Histopathological alterations included metaplasia of tracheal epithelial. The NOAEL was considered to be 50 mg/kg/day, based on increases in relative kidney weight (ECHA, 2011).

Since the available systemic toxicity data on *p*-cresol allows for the

determination of a NOAEL for the repeated dose toxicity endpoint, a NOAEL of 50 mg/kg/day was determined from the 90-day gavage study in rats.

Therefore, the *p*-cresol MOE for the repeated dose toxicity endpoint can be calculated by driving the *p*-cresol NOAEL in mg/kg/day by the total systemic exposure to *p*-cresol, 50/0.00016, or 312500.

In addition, the total systemic exposure to *p*-cresol (0.16 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1.1. Derivation of reference dose (RfD). 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, 2020) and a reference dose of 0.50 mg/kg/day.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for *p*-cresol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 50 mg/kg/day by the uncertainty factor, 100 = 0.50 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/19/20.

11.1.3. Reproductive toxicity

The MOE for *p*-cresol is adequate for the reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on *p*-cresol. In a GLP-compliant developmental toxicity study (according to TSCA health effects test guidelines for specific organ/tissue toxicity–developmental toxicity), pregnant female New Zealand white rabbits were administered *p*-cresol via oral gavage at doses of 0, 5, 50, or 100 mg/kg/day in corn oil during GDs 6–18. The treatment groups consisted of 14 animals/dose, and the control group consisted of 28 animals. All animals were euthanized on GD 29. The reproductive toxicity parameters (uterus, number of corpora lutea, implantation sites, resorptions, and dead/live fetuses) were assessed. All live fetuses were counted, sexed, weighed, and examined for external, skeletal, and visceral malformations. Maternal toxicity was reported at 50 and 100 mg/kg/day, which included mortality at 50 mg/kg/day (2/13; 14.3%) and 100 mg/kg/day (5/14; 35.7%) and clinical signs of toxicity (hypoactivity, gasping, cyanosis, and labored and rapid audible respiration), and ocular discharge. No adverse treatment-related effects were reported for maternal body weight, food consumption, and necropsy at any dose level. There were no treatment-related adverse effects reported for gestational parameters or on the development of fetuses, including numbers of corpora lutea, implantation sites, live and dead fetuses, sex ratio, and fetal malformations at any dose level. Embryotoxicity or teratogenicity were not observed up to the highest dose level. Therefore, the NOAEL for maternal toxicity was considered to be 5 mg/kg/day, based on mortality and clinical signs observed among the higher dose group dams. The NOAEL for developmental toxicity was considered to be 100 mg/kg/day, the highest dose tested (EPA, 1988a).

Another developmental toxicity study on *p*-cresol was conducted in rats (see Table 1; EPA, 1988b), which concluded a similar developmental toxicity NOAEL of 175 mg/kg/day. The most conservative NOAEL of 100 mg/kg/day from the rabbit study was selected for the developmental toxicity endpoint.

Therefore, the *p*-cresol MOE for the developmental toxicity endpoint can be calculated by dividing the *p*-cresol NOAEL in mg/kg/day by the total systemic exposure for *p*-cresol, 100/0.00016, or 625000.

There are sufficient fertility data on *p*-cresol. A GLP-compliant, 2-generation reproductive toxicity study (according to TSCA health effects test guideline for specific organ/tissue toxicity-reproduction/fertility effects) was conducted in Sprague Dawley rats. Groups of 25 rats/sex/dose (for both F0 and F1 generations) were administered via oral gavage *p*-cresol at doses of 0, 30, 175, or 450 mg/kg/day in corn oil. Animals were dosed for 5 days per week for 10 weeks (F0 generation) and 11 weeks (F1 generation) during the premating period. After the premating period, F0 male and female rats were dosed daily through mating for 3 weeks, females were dosed daily throughout the gestation and lactation periods for up to day 21 post-partum, and F0 males were dosed until necropsy. Groups of F1 rats were treated similarly to the parental generation to produce the F2 generation. At 450 mg/kg/day, mortality was reported for both F0 and F1 generation male (28%–36%) and female (32%–40%) animals. Treatment-related statistically significant decreases in body weight and bodyweight gains were reported primarily in F0 and F1 males and F0 females at 450 mg/kg/day. Additionally, statistically significant decreases in bodyweight gain extended to the 175 mg/kg/day F0 males and females. A statistically significant decrease in food consumption was also noted in F0 and F1 animals at 450 mg/kg/day. Clinical signs of toxicity were reported in F0 and F1 parental rats (hypoactivity, ataxia twitches, tremors, prostration, urine stains, and audible respiration) at 450 mg/kg/day, and statistically significant increased incidences of perioral wetness were reported in both the sexes at 175 and 450 mg/kg/day. Perinasal encrustation and urogenital wetness were also noted in F0 and F1 females at 450 mg/kg/

Table 1
Additional developmental toxicity study in rats.

Duration in detail	GLP/Guideline	No. of animals/dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
GD 6–15	GLP-Compliant/EPA TSCA testing guidelines (1984, 1985, 1986a, 1987b) and to the EPA Cresol Test Rule (1983b, 1986b, 1986c; 1987a)	Sprague Dawley (CD) rats. 25 pregnant female rats/group and 50 control females	Oral gavage (Corn oil)	0, 30, 175, or 450 mg/kg/day (Purity: 98.93%)	Maternal and developmental toxicity NOAEL = 175 mg/kg/day	• At 450 mg/kg/day, significant reduction in maternal bodyweight gain observed • Clinical signs of toxicity at 450 mg/kg/day: hypoactivity, ataxia, tremors, twitches, prone positioning, audible respiration, and perioral wetness • Fetotoxicity at 450 mg/kg/day, as evidenced by reduced ossification in 3 skeletal districts (bilobed cervical centrum number 6, reduction in the number of ossified caudal segments, and unossified sternebrae 5) and reduced fetal body weight	EPA, 1988b; sub-reference 06/29; ECHA, 2011

day. At 450 mg/kg/day, 3/18 F1 males that survived until the end of treatment exhibited seminiferous tubule atrophy and degeneration as well as decreased epididymal sperm. Microscopic observations of decreased number of spermatozoa that were reported in a small number of animals failed to reveal a target organ or a mechanism of toxicity; hence, the observed effects from necropsy and histopathology of F1 animals were not considered to be treatment-related. No treatment-related findings at necropsy or histopathological findings were observed in F0 and F1 animals that survived until the end of treatment. No treatment-related adverse effects were reported on estrous cycling, mating, fertility, gestation, or sperm parameters at any dose level in both F0 and F1 generations. *p*-Cresol caused an increase in stillbirths in both the F1 and F2 generations for F1 pups at 175 mg/kg/day (but not 450 mg/kg/day) and F2 pups at 30 and 450 mg/kg/day (but not at 175 mg/kg/day). In the F2 (but not F1) group, live birth indices were reduced at 30 and 450 mg/kg/day (but not 175 mg/kg/day). There was no clear dose-dependent effect in both generations. Pup survival indices in both generations were not affected by treatment at any dose level. Therefore, the NOAEL for parental toxicity was considered to be 30 mg/kg/day, based on clinical signs of toxicity at concentrations ≥175 mg/kg/day, increased mortality, and reduced bodyweight gain at 450 mg/kg/day. Based on a decrease in epididymal sperm, and a microscopic decrease in the number of spermatozoa in F1 males, the most conservative NOAEL of 175 mg/kg/day was selected for the fertility endpoint (EPA, 1989b; sub-reference 11/13). See Table 1 for additional studies.

Therefore, the *p*-cresol MOE for the fertility endpoint can be calculated by dividing the *p*-cresol NOAEL in mg/kg/day by the total systemic exposure for *p*-cresol, 175/0.00016, or 1093750.

In addition, the total systemic exposure to *p*-cresol (0.16 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Kavlock (1990); Oglesby (1992); Izard et al.,(1992).

Literature Search and Risk Assessment Completed On: 04/06/20.

11.1.4. Skin sensitization

Based on the available data and application of the DST, *p*-cresol does not present a concern for skin sensitization under current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for *p*-cresol. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly, whereas its metabolite is expected to be reactive (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), the sensitization potential of *p*-cresol was found to be inconclusive. In a Draize test and Open Epicutenous Test (OET) conducted in guinea pigs, *p*-cresol did not result in reactions indicative of skin sensitization (ECHA, 2011; Klecak, 1985). In a human maximization test, no skin sensitization reactions were reported (RIFM, 1972). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/06/20.

11.1.5. Skin depigmentation

For applications on areas of skin, depigmentation may be a concern at current use levels. Skin depigmentation data are needed to complete the safety assessment.

11.1.5.1. Risk assessment. In addition to systemic toxicity, *p*-cresol (0.5% in acetone), when applied on the backs of mice 3 times weekly for 6 weeks, resulted in depigmentation of skin and hair (Shelley, 1974). The Cosmetics Ingredients Review (CIR) panel has reviewed the toxicity data available on *p*-cresol, including the study on depigmentation, and concluded that a safe-use level for cosmetics use could not be derived. In addition, the CIR panel also concluded that available data were insufficient to support the safety of *p*-cresol (CIR, 1994). There was no information available on safe doses because this was a single study, in which adverse effects were seen at the lowest dose. Thus, based on skin and hair depigmentation, the LOAEL for this study was considered to be 0.5%. The LOAEL is adjusted by a safety factor of 10 for a NOAEL of 0.05%. The NOAEL is adjusted by a safety factor of 10 for a maximum safe-use level of 0.005%.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/02/20.

11.1.6. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and the available human study data, *p*-cresol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.6.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Photoallergenicity of *p*-cresol was evaluated in human volunteers. Topical application of a 1% solution of *p*-cresol in petrolatum via 24-h occlusive patch did not result in photoallergenic reactions in any of the volunteers (RIFM, 1982). Based on the lack of absorbance in the range of interest and the results of the photoallergenicity study in humans, *p*-cresol does not present a concern for phototoxicity and photoallergenicity.

11.1.7. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/30/20.

11.1.8. Local Respiratory Toxicity

The MOE could not be calculated due to the lack of appropriate data. The exposure level for *p*-Cresol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.8.1. Risk assessment. There are insufficient inhalation data available on *p*-cresol. Based on the Creme RIFM Model, the inhalation exposure is 0.0018 mg/day. This exposure is 777.8 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References:

Chin (1941); Bieniek (1997); EPA, 1978; Campbell (1941); Hagmar, 1988a; Hagmar, 1988b; Pero (1988); Chin (1941); Bieniek (1997); EPA, 1949; EPA, 1978; Campbell (1941); Bieniek (1994); Chin (1941); Uzhdavini (1974); Uzhdaini (1972); EPA, 1978; Campbell (1941); ECHA, 2011c; ECHA, 2011a; ECHA, 2011b.

Literature Search and Risk Assessment Completed On: 04/03/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *p*-cresol was performed following the RIFM Environmental Framework (Salvito, 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, *p*-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 *p*-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, 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), *p*-cresol presents 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.

11.2.3.3. Other available data. *p*-Cresol has been registered under REACH, and the additional data is available (ECHA, 2011c):

The ready biodegradability of the test material was evaluated using the Modified MITI Test (I) according to the OECD 301 C guideline. Biodegradation of 95% was observed after 40 days.

The inherent biodegradability of the test material was evaluated using the Zahn-Wellens Test according to the OECD 302 B guideline. Biodegradation of 100% was observed after 10 days.

The inherent biodegradability of the test material was evaluated using the Zahn-Wellens Test according to the OECD 302 B guideline. Biodegradation of 96% was observed after 5 days.

The acute toxicity of *p*-cresol to fish was determined with a static bioassay on several freshwater species. The highest toxicity was reported with *Salmo trutta* with a 96-h LC50 value of 4.4 mg/L, based on nominal concentration.

The chronic toxicity of *p*-cresol to fish was tested with *Pimephales promelas* in an Early-Life Stage Toxicity Test equivalent to OECD Guideline 210, under flow-through conditions. The 32-day NOEC was reported to be 1.35 mg/L.

The short-term toxicity of *p*-cresol to *Daphnia magna* was measured according to German Guideline DIN 38412 part 11, under static conditions. The 48-h EC50 value based on nominal concentration was reported to be 7.7 mg/L.

The long-term toxicity of *p*-cresol to aquatic invertebrates was determined according to the preliminary guideline proposal of the German Umweltbundesamt from 1984, under semi-static conditions. After 21 days of exposure, a NOEC value of 1 mg/L was determined based on nominal concentration.

The toxicity of *p*-cresol to the algae was determined according to DIN 38412 part 9 guidelines, under static conditions. Based on nominal concentrations, a 48-h EC50 (growth rate) of 21 mg/L was reported based on nominal concentration.

11.2.3.3.1. Risk assessment refinement. Since *p*-cresol has passed the screening criteria (Tier 1), measured data from REACH is included in this document for completeness only and has not been used in PNEC derivation.

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)**	129.4			1000000	0.1294	

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito, 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.0	2.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<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 0.1294 μg/L. The revised PEC/PNECs are not applicable. The material was cleared at the screening-level 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: 04/03/20.

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 05/07/21.

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.

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