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Short Review

RIFM fragrance ingredient safety assessment, *m*-cresol, CAS Registry Number 108-39-4

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Version: 103020. This version replaces any previous versions.
Name: *m*-Cresol
CAS Registry Number: 108-39-4

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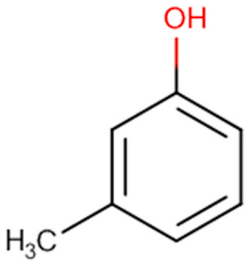

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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, 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).

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*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.

m-Cresol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *m*-cresol is not genotoxic and 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 non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; *m*-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, and the exposure to *m*-cresol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; *m*-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: m-Cresol; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day.	NTP (1992)
Reproductive Toxicity: Developmental toxicity: 175 mg/kg/day Fertility: 175 mg/kg/day.	(EPA, 1989; US EPA, 2016; NTRL, 2000)
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.	Yamano (2007)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 96% in 10 days (OECD 302B)	(ECHA REACH Dossier: m-Cresol; ECHA, 2011)
Bioaccumulation: Screening-level: 9.124 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 151.8 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 151.8 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.1518 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name**: *m*-Cresol
2. **CAS Registry Number**: 108-39-4
3. **Synonyms**: *m*-Cresylic acid; 1-Hydroxy-3-methylbenzene; 3-Hydroxytoluene; 1-Methyl-3-hydroxybenzene; 3-Methylphenol; *m*-Methylphenol; Phenol, 3-methyl-; meta-Cresol; *m*-Cresol
4. **Molecular Formula**: C_7H_8O
5. **Molecular Weight**: 108.14
6. **RIFM Number**: 6106
7. **Stereochemistry**: Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 201 °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}:** LogK pdms/w = 0.352 (n = 12) (Xia, 2007), 1.97 (Smith, 2002), 1.96 (Patel, 2002), 1.96 (Smith, 2002), 1.98 (Abraham, 1995), 2.06 (EPI Suite)
4. **Melting Point:** 15.69 °C (EPI Suite)
5. **Water Solubility:** 8890 mg/L (EPI Suite)
6. **Specific Gravity:** 1.034 (FMA)
7. **Vapor Pressure:** 0.109 mm Hg at 20 °C (EPI Suite v4.0), 0.167 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient (80.4 L mol^{-1} · cm^{-1} under neutral conditions) is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless or yellow to brown liquid with dry, tarry, medicinal-leathery, phenolic odor

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v2.0)

1. 95th Percentile Concentration in Hydroalcoholics: 0.000052% RIFM (2019)
2. Inhalation Exposure*: <0.0001 mg/kg/day or 0.0000027 mg/day RIFM (2019)
3. Total Systemic Exposure**: 0.000097 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: 80%

No data are available on the skin absorption for *m*-cresol. Therefore, dermal absorption is estimated using the Kroes approach (Kroes, 2007). Based on the molecular weight of 108.1 Da and the measured log K_{ow} of 1.98 (Abraham and Rafols, 1995), dermal absorption is expected to be high. Hence, conservatively, an absorption value of 80% can be used for *m*-cresol.

Jmax Table (From the RIFM SAM model):

	Parent
Name	*m*-cresol
J_{max} (μg/cm^2/h)	1299.711[1]
Skin Absorption Class	≤80%

[1] J_{max} was calculated based on measured log K_{OW} = 1.98 (Abraham and Rafols, 1995) and Solubility = 22700 mg/L (consensus model).

Roberts (1977); **ECHA Dossier:** m-Cresol (ECHA, 2011; **accessed 02/07/20):** In an *in vitro* study, the human epidermis was used to determine the permeability coefficient of *m*-cresol using spectrophotometric analysis. The *m*-cresol was exposed up to 250 min. The permeability coefficient was reported as 2.54×10^{-4} cm/min, and the lag time for 0.4% w/v concentration was 15 min.

2. Oral: 84%

NICNAS, 2014 **(accessed 02/07/20);** NTRL, 1985 **(accessed 02/07/20):** When rats (strain, sex, and number of animals not specified) were treated with *m*-cresol via gavage, at least 65%–84% of the administered dose was absorbed within 24 h based on the recovery in the urine.

3. Inhalation: Assumed 100%

6. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v3.2
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
3. **Read-across Justification**: None

7. Metabolism

m-Cresol is well absorbed through the respiratory, gastrointestinal tract, and intact skin in animals and humans. It is expected to be distributed throughout the body (OECD, 2003; NICNAS, 2014). When dogs were treated with *m*-cresol orally, it was reported to be distributed in the blood, liver, brain, lungs, kidneys, or other organs. When female rats were exposed to 10 mg/m^3 of *m*-cresol for 4 h/day up to 4 months, it reached a concentration of 12.2 μg/g in lung tissue, which indicated that *m*-cresol is well absorbed through the inhalation route (OECD, 2015). When 20 mL of *m*-cresol was accidently spilled on a human infant head, death was observed after 4 h, and the material was detected in the blood (120 mg/L), liver, brain, and urine, which indicates that *m*-cresol has a potential to penetrate through the skin (IPCS, 1995). *m*-Cresol is expected to be metabolized in the liver (US ECHA, 2016; NICNAS, 2014). The primary metabolic pathway is in conjugation with glucuronic acid or inorganic sulfates at the hydroxy group and excreted as conjugates in the urine. Additionally, *m*-cresol is excreted in the bile, which then undergoes enterohepatic circulation (OECD, 2003; NTP, 1992; NTP, 2008; NICNAS, 2014; NTRL, 1985). The primary route of elimination is through urine because of the reduced renal absorption due to the ionization of conjugated metabolites. Minor metabolites may be formed through ring hydroxylation to result in conjugated 2,5 or 3,4-dihydroxy toluene (EFSA, 2006; NICNAS, 2014). When rabbits were treated with *m*-cresol via gavage at a single dose of 500 mg/kg, ether glucuronide (60%–72%), ethereal sulfate (10%–15%), free cresol (1%), 2,5-dihydroxytoluene (3%), and a trace amount as 3,4-dihydroxytoluene were recovered in the urine (Bray, 1950; OECD, 2003; NTP, 1992; IPCS, 1995; NICNAS, 2014; NTRL, 1985; ATSDR, 2008; Wiley, 1999). When female rabbits were treated with *m*-cresol via gavage at a single dose of 290 mg/kg for 6 days, 22% of the administered dose was conjugated with sulfate in the urine (Williams, 1938; ECHA, 2011; NTP, 2008; IPCS, 1995; NTRL, 1985). When albino rabbits were treated with *m*-cresol via gavage, the urinary excretion of glucuronic acid and organic sulfates were increased after the oral administration. Normal daily urinary excretion of glucuronic acid in rabbits averaged about 35 mg (Deichmann, 1943; IPCS, 1995). When guinea pigs were treated with *m*-cresol via subcutaneous injection at a single dose range of 7.2–10 mg, 20% of the administered dose was eliminated as unchanged *m*-cresol in the urine (Bardodej, 1961).

Additional References: None.

8. Natural occurrence (discrete chemical) or composition (NCS)

m-Cresol is reported to occur in the following foods by the VCF*:

Cheese, various types	Licorice (*Glycyrrhiza* species)
Cocoa category	*Mangifera* species
Coffee	Pork
Fish	Salami
Katsuobushi (dried bonito)	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 01/16/20 (ECHA, 2011).

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, *m*-cresol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of *m*-cresol was assessed in an Ames assay conducted in compliance with GLP regulation in accordance with OECD TG 471 using the standard preincubation method. *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and *Escherichia coli* WP2uvrA/pKM101 were treated with *m*-cresol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No increases in the number of revertant colonies were observed in any of the tester strains at the concentrations tested (ECHA, 2011). Under the conditions of the study, *m*-cresol was considered not mutagenic in the Ames test.

The clastogenicity of *m*-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 lung cells were treated with *m*-cresol in DMSO at concentrations up to 1100 μg/mL in the presence and absence of metabolic activation. Statistically significant increases in the frequency of cells with structural and chromosomal aberrations were observed with and without S9 metabolic activation test conditions (ECHA, 2011). Under the conditions of the study, *m*-cresol was considered to be clastogenic in the *in vitro* chromosome aberration assay. In order to verify the biological relevance of the *in vitro* results, follow-up *in vivo* studies were considered for the safety assessment of *m*-cresol. The clastogenic activity of *m*-Cresol was assessed in an *in vivo* chromosomal aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 475. Groups of male and female ICR mice were dosed *m*-cresol in 5 mL of corn oil by oral gavage at the concentrations of 0, 96, 320, 960 mg/kg body weight (b.w.). Animals were euthanized at 6, 24, and 48 h after administration, and the femora were removed. (ECHA, 2011). Under the conditions of the study, *m*-cresol did not have any clastogenic effect in the *in vivo* chromosomal aberration study. Additionally, a mixture of *m*-/*p*-cresol was evaluated for the induction of micronuclei in peripheral blood erythrocytes of male and female mice following 13 weeks of exposure in the diet (NTP, 1992). No significant increase in the frequency of micronucleated erythrocytes was observed.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/26/20.

11.1.2. Repeated dose toxicity

The MOE for *m*-cresol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on *m*-cresol.

In an OECD TG 408 and GLP-compliant subchronic toxicity study, 30 Sprague Dawley rats/sex/dose were treated with *m*-cresol via gavage at doses of 0 (vehicle: corn oil), 50, 150, and 450 mg/kg/day for 13 weeks (daily). No recovery group was included. No treatment-related adverse effects were reported on mortality, food consumption, ophthalmoscopy, hematology, clinical biochemistry, urinalysis, necropsy, organ weights, or histopathology up to the highest tested dose. Clinical findings such as lethargy, tremors, hunched posture, and rough hair coats after dosing were reported in both sexes at 450 mg/kg/day. Significantly decreased body weight was reported in males at 450 mg/kg/day (20%–25%) and 150 mg/kg/day (10–15%). Significantly decreased bodyweight gain was reported in males at 450 mg/kg/day and 150 mg/kg/day. Based on clinical findings (lethargy, tremors, hunched posture, and rough hair coats) at 450 mg/kg/day, as well as decreased body weight and bodyweight gain at concentrations ≥150 mg/kg/day, the no observed adverse effect level (NOAEL) for repeated dose toxicity was considered to be 50 mg/kg/day (NTRL, 1988).

In a subchronic repeated dose neurotoxicity study (non-guideline and non-GLP-compliant), 10 CD rats/sex/dose were treated with *m*-cresol via gavage at doses of 50, 150, and 450 mg/kg/day for 13 weeks (daily). No recovery group was included. The control group consisted of 20 CD rats/sex and were administered only the vehicle (corn oil). Mortality was reported in 1 female at 450 mg/kg/day due to aspiration. Histopathology examination of this individual revealed necrosis and inflammation of the trachea and/or larger bronchi. Death may have occurred due to pneumonia or pulmonary edema. Clinical findings such as myotonus, rapid respiration, hypoactivity, and clonic convulsions were reported in both sexes at 450 mg/kg/day. Low body posture, labored respiration, and urine-wet abdomens were reported at 450 mg/kg/day shortly after dosing. Tremors were reported in both sexes at concentrations ≥150 mg/kg/day. Myoclonus was reported in males at concentrations ≥150 mg/kg/day and in females at 450 mg/kg/day. Respiratory effects such as rales and labored respiration were reported with increased incidence in females at 450 mg/kg/day during week 1 and were likely due to inhalation or aspiration of the test material. Urination was increased in females at 450 mg/kg/day. Based on mortality and clinical findings of neurotoxicity, tremors and myoclonus at concentrations ≥150 mg/kg/day and low body posture, labored respiration, urine-wet abdomens, myotonus, rapid respiration, hypoactivity, clonic convulsions, rales, increased urination, and decreased diarrhea at 450 mg/kg/day, the NOAEL for neurotoxicity was considered to be 50 mg/kg/day (RIFM, 1986; US EPA, 2016; US EPA, 1988).

Toxicity data on *m*-cresol have been extensively reviewed by several organizations, among which Health Canada provides the most recent review (Health Canada, 2016). Repeated dose toxicity for *m*-/*p*-cresol was 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 *m*-/*p*-cresol from the diet. Such findings have been reported from studies on *m*-/*p*-cresol or mixed cresols from short- or long-term exposures. It was concluded that respiratory tract

lesions reported in studies with *m*-/*p*-cresol or mixed cresols were due to local effects resulting from inhalation of *m*-/*p*-cresol from the diet and not as a result of systemic toxicity. Although the NTP presents equivocal evidence for carcinogenicity due to *m*-/*p*-cresol exposure, an ECHA-CoRAP evaluation suggests that the available data do not present a carcinogenic hazard to humans (NTP, 2008; ECHA, 2016).

Based on the 13-week studies on *m*-cresol, the NOAEL was determined to be 50 mg/kg/day. This NOAEL was also concluded from reviews on *m*-cresol by US EPA (1988) and WHO (1996). Table 1 below lists the findings of additional studies.

Therefore, the *m*-cresol acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the *m*-cresol NOAEL in mg/kg/day by the total systemic exposure for *m*-cresol acetate, 50/0.000097, or 515464.

In addition, the total systemic exposure to *m*-cresol acetate (0.097 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.

Additional References: Health Canada (2016); ECHA, 2011; EFSA, 2006; ATSDR, 2008; OECD, 2003; NTP, 1992; US EPA, 2016; NCBI, 2020 (accessed 02/11/20); IPCS, 1995 (accessed 02/11/20); NTP, 1991; MDEQ (Michigan Department of Environmental Quality), 2005; NIH, 2009; USA EPA, 1988; NICNAS, 2014; NTRL, 1985.

Literature Search and Risk Assessment Completed On: 02/14/20.

11.1.3. Reproductive toxicity

The MOE for *m*-cresol is adequate for the fertility and developmental toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are sufficient fertility and developmental toxicity data on *m*-cresol.

In a 2-generation reproductive toxicity study (EPA TSCA 1984 testing guidelines and GLP-compliant), 25 Sprague Dawley rats/sex/dose were treated with *m*-cresol via gavage at doses of 0 (vehicle: corn oil), 30, 175, and 450 mg/kg/day for 10 weeks (5 days/week). After the initial 10-week exposure period, animals were randomly paired for a 3-week mating period. During the mating period, the dosing regimen was changed from 5 days/week to 7 days/week. For females, dosing continued 7 days/week during gestation and lactation. Twenty-five F1 offspring/sex/dose were randomly selected to continue exposure and were mated to produce an F2 generation. Dosing began between postnatal days (PNDs) 28 and 40. F1 parental animals were dosed under the same schedule as the F0 generation parental animals for an 11-week premating period, a 3-week mating period, during gestation, and through lactation. In the F0 generation, mortality was reported in males (7/25) and females (5/25) at 450 mg/kg/day during the pre-mating dosing period. At necropsy, animals that were found dead showed brain hemorrhage, intestinal dilation and distention, diffuse or multifocal color changes in the lungs, and crust on the skin at 450 mg/kg/day. A decreased number of sperm, atrophied seminal vesicles, congestion, and rhinitis, and lung congestion were reported in dead males at 450 mg/kg/day. Congestion in the lung and congestion of the meningeal vessels were reported in dead females at 450 mg/kg/day. Clinical findings such as hypoactivity, ataxia, twitches, tremors, prostration, unkempt appearance, urine stains, audible respiration, peri-nasal encrustation, perioral wetness, and red perioral wetness were reported at 450 mg/kg/day. Significantly decreased body weight was reported in F0 males at 450 mg/kg/day throughout the pre-mating period and mating period (weeks 11, 12, and 13). Significantly decreased body weight was reported in F0 females at 450 mg/kg/day during the pre-mating through lactation period; however, reduction in body weight was within 10% of

Table 1
Additional studies.

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
28 days (additionally 2 weeks recovery period was maintained for control and 1000 mg/kg/day)	OECD 407/GLP	7 Crj: CD(SD rats/sex/dose	Oral: gavage	0, 100, 300 and 1000 mg/kg/day	300 mg/kg/day	Clinical signs of neurotoxicity and significantly decreased body weight at 1000 mg/kg/day. Significant increase in liver weights and histopathological changes in the liver reported at 1000 mg/kg/day	Koizumi (2003)
28 days	Not reported	10 male rats/dose	Oral:feed	0, 20, 150, 500 mg/kg diet (approx. 0, 1.86, 13.95 or 45.8 mg/kg/day)	45.8 mg/kg/day	No adverse effects reported	ECHA (2011)
28 days	Not reported	Rats (both sexes), no of animals and strain not specified	Oral: gavage	0, 300, and 1000 mg/kg/day	300 mg/kg/day	Clinical findings (CNS effects-salivation and tremors) and decreased bodyweight gain in both sexes at 1000 mg/kg/day	Hasegawa (2003)
28 days	NTP study; GLP: Yes	5 F344/N rats/sex/dose	Oral: feed	0, 300, 1000, 3000, 10000, or 30000 ppm (equal to males: 0, 25, 85, 252, 870, 2470 mg/kg/day; females: 0, 25, 82, 252, 862, 2310 mg/kg/day)	252 mg/kg/day	Increased liver weights at concentrations ≥10000 ppm and decreased bodyweight gain and decreased food consumption, minimal to mild uterine atrophy in 4/5 females at 30000 ppm	NTP (1992)
28 days	NTP study; GLP: Yes	5 B6C3F1 mice/sex/dose	Oral: feed	0, 300, 1000, 3000, 10000 or 30000 ppm (equal to males: 0, 53, 193, 521, 1730, and 4710 mg/kg/day; females: 0, 66, 210, 651, 2080, and 4940 mg/kg/day)	521 mg/kg/day (males), 651 mg/kg/day (female)	Mortality, and clinical findings at concentrations ≥10000 ppm; decreased bodyweight gain, decreased food consumption, clinical findings (lethargy, tremor, and hypothermia), atrophy of mammary glands, ovaries, and uterus at 30000 ppm	NTP (1992)
6 weeks	Not reported; mouse hair pigmentation study	5 female CBA/J agouti mice	Dermal	0.5% mist in acetone was applied	5%	No adverse effects reported	CIR (2006)

controls throughout the study. Significantly decreased (7%–9%) litter body weight was reported in F1 male pups on PNDs 14 and 21 at 450 mg/kg/day. In the F1 parental animals, mortality was reported in males (3/25) and in females (10/25) at 450 mg/kg/day. At necropsy, animals that were found dead showed focal or multifocal color changes in the lungs, congestion of the nares, nasal cavity, and lungs, crusting around the nose, stained skin, and alopecia at 450 mg/kg/day. Clinical findings such as hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, and perioral wetness were reported in both sexes of F1 adults at 450 mg/kg/day. Additionally, increased incidences of labored respiration and peri-nasal wetness were reported in F1 adult females at 450 mg/kg/day, and increased incidences of perioral wetness were reported in F1 adult females at 175 mg/kg/day, which indicate salivation. Significantly decreased body weight was reported in both sexes at 450 mg/kg/day during the pre-exposure period and F1 parental animals; this bodyweight reduction was continued to be significant throughout the pre-mating and mating exposure periods. Significantly decreased body weight was reported in F1 adult females at 450 mg/kg/day during pre-mating, mating, gestation, and lactation periods; however, the decreased body weights remained within 10% in comparison to controls. Significantly decreased body weight was reported in F1 adult males at 175 mg/kg/day from week 1 to week 10 and week 13 to week 14. Significantly decreased body weight was reported in F1 adult males at 30 mg/kg/day from week 1 to week 14. Significantly decreased body weight was reported in F1 adult females at 30 mg/kg/day from week 1 to week 6 and week 9 to week 11. Significantly decreased (9–12%) litter body weight for F2 male and female pups on PNDs 14 and 21 were reported at 450 mg/kg/day. Significantly decreased lactation index was reported in F2 pups at 450 mg/kg/day. Pup deaths were increased on PND 21 at 450 mg/kg/day; however, half of the deaths were not treatment-related, but due to the death of their mother, and these pups were euthanized after the death of their mother. There was a lack of treatment-related adverse effects reported on reproductive parameters in either of the 2 generations at any dose level, but based on mortality seen at the highest dose in parental animals, the NOAEL for fertility was considered to be 175 mg/kg/day. Based on pup mortality, decreased pup body weight in F1 and F2 pups, and decreased lactation index in F2 pups at 450 mg/kg/day, the NOAEL for developmental toxicity was considered to be 175 mg/kg/day (EPA, 1989; ECHA, 2016; NTRL, 2000).

Therefore, the *m*-cresol MOE for the developmental toxicity endpoint can be calculated by dividing the *m*-cresol NOAEL in mg/kg/day by the total systemic exposure for *m*-cresol, 175/0.000097, or 1804124.

The *m*-cresol MOE for the fertility endpoint can be calculated by dividing the *m*-cresol NOAEL in mg/kg/day by the total systemic exposure for *m*-cresol, 175/0.000097, or 1804124.

In addition, the total systemic exposure to *m*-cresol (0.097 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: ECHA, 2011; OECD, 2015; EFSA, 2006; NICNAS, 2014; NCBI, 2020; IPCS, 1995; ATSDR, 2008; Health Canada, 2016; Wiley, 1999

Literature Search and Risk Assessment Completed On: 02/26/20.

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2 [OECD, 2018]). In a murine local lymph node assay (LLNA), the study details were inconclusive for sensitization (Yamano, 2007). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 2 provides the maximum acceptable concentrations for *m*-cresol that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/05/20.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available

Table 2
Maximum acceptable concentrations for *m*-cresol that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU[b]
2	Products applied to the axillae	0.021%	NRU[b]
3	Products applied to the face using fingertips	0.41%	NRU[b]
4	Fine fragrance products	0.39%	5.2×10^{-5}%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	NRU[b]
6	Products with oral and lip exposure	0.23%	0.0015%
7	Products applied to the hair with some hand contact	0.79%	NRU[b]
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	8.0×10^{-4}%
10	Household care products with mostly hand contact	2.7%	NRU[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	3.0×10^{-5}%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] NRU (No reported use).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

for *m*-cresol in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance in the critical range, *m*-cresol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm, with a peak at 280 nm and absorbance tailing to about 290 nm. The molar absorption coefficient for the maximum absorbance between 290 and 700 nm is 80.4 L mol^{-1} · cm^{-1} at 290 nm under neutral conditions. This is well 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: 02/18/20.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on *m*-Cresol. Based on the Creme RIFM Model, the inhalation exposure is 0.0000027 mg/day. This exposure is 518518 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: Hagmar, 1988a; Hagmar, 1988b; Pero (1988); Chin (1941); Bieniek (1997); EPA, 1949; EPA, 1978; Campbell (1941).

Literature Search and Risk Assessment Completed On: 02/26/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *m*-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, *m*-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 *m*-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), *m*-cresol 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

m-Cresol has been registered under REACH with the following additional data available at this time (ECHA, 2011):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301 D guideline. Biodegradation of 90% was observed after 28 days.

The inherent biodegradability of the test material was evaluated according to the OECD 302B guideline. Biodegradation of 96% was observed after 10 days.

The acute toxicity of the test material to *Daphnia* was determined according to the EPA OPP 72-2 guideline under flow-through conditions. The 48-h LC50 value based on measured concentration was reported to be > 99.5 mg/L.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	151.8			1000000	0.1518	

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 Environmental Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.98	1.98
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	No VoU
Risk Characterization: PEC/PNEC	**< 1**	**NA**

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

The RIFM PNEC is 0.1518 μg/L. The revised PEC/PNECs for EU and NA (No VoU) 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 volumes of use.

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

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 05/31/20.

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.

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