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Short review

RIFM fragrance ingredient safety assessment, *o*-cresol, CAS Registry Number 95-48-7

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Name: *o*-Cresol CAS Registry Number: 95-48-7

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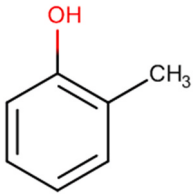

Abbreviation/Definition List:

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).

*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.

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Summary: The existing information supports the use of this material as described in this safety assessment.

o-Cresol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *o*-cresol is not genotoxic and provide a calculated margin of exposure (MOE) > 100 for the reproductive toxicity endpoint. The repeated dose and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to *o*-cresol is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. There is no concern for depigmentation at current use levels. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; *o*-Cresol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *o*-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: *o*-Cresol; ECHA, 2011b; US EPA, 1988a; NTP, 1992b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.	
Reproductive Toxicity: Developmental NOAEL = 100 mg/kg/day. Fertility NOAEL = 773 mg/kg/day.	US EPA (1988c)
Skin Depigmentation: NOAEL = 0.5%; Maximum Safe-Use Level: 0.05%.	Shelley (1974)
Skin Sensitization: No safety concerns at current, declared use levels. Exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not 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: 100% (OECD 302B)	(ECHA REACH Dossier: o-Cresol; ECHA, 2011b)
Bioaccumulation: Screening-level: BCF: 10.7	(ECHA REACH Dossier: o-Cresol; ECHA, 2011b)
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 and Europe: not applicable; cleared at screening-level	

1. Identification

1. Chemical Name: *o*-Cresol
2. CAS Registry Number: 95-48-7
3. Synonyms: *o*-Cresylic acid; 2-Hydroxy-1-methylbenzene; 1-Hydroxy-2-methylbenzene; *o*-Hydroxytoluene; *o*-Methylphenol; Phenol, 2-methyl-; 2-Methylphenol; ｸﾚｿﾞｰﾙ; ortho-Cresol; *o*-Cresol
4. Molecular Formula: C_7H_8O
5. Molecular Weight: 108.14
6. RIFM Number: 1106
7. Stereochemistry: One possible stereoisomer

2. Physical data

1. **Boiling Point:** 191 °C (Fragrance Materials Association [FMA]), 190.8 °C (EPI Suite)

2. **Flash Point:** 81 °C (Globally Harmonized System), 171 °F; CC (FMA)
3. **Log K_{OW}:** 1.92 (Smith, 2002), 1.94 (Huang, 2003), 1.98 (Abraham, 1995), 1.95 (Smith, 2002), 1.95 (Patel, 2002), 2.06 (EPI Suite)
4. **Melting Point**: 31 °C (FMA), 15.69 °C (EPI Suite)
5. **Water Solubility:** 9066 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.15 mm Hg at 20 °C (EPI Suite v4.0), 0.2 mm Hg at 20 °C (FMA), 0.25 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00011% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.0000001 mg/kg/day or 0.0000085 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.00039 mg/kg/day (RIFM, 2016)

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 3.1	OECD QSAR Toolbox v 3.2
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

No relevant data available for inclusion in this safety assessment.
Additional References:

None.

8. Natural occurrence

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

Asparagus (*Asparagus officinalis* L.)
Beans
Beer
Buckwheat
Cardamom (*Ellettaria cardamomum* Maton.)

*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, 2011b).

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

11.1.1.1. Risk assessment. The mutagenic activity of *o*-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 *o*-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, 2011b). Under the conditions of the study, *o*-cresol was not mutagenic in the Ames test.

The clastogenicity of *o*-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 *o*-cresol in DMSO at concentrations up to 3000 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 (US EPA, 1988a). Under the conditions of the study, *o*-cresol was considered to be clastogenic in the *in vitro* chromosome aberration assay.

The clastogenic activity of *o*-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, 5000, 10000, and 20000 ppm were administered. Mice from each dose level were euthanized at 13 weeks, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (NTP, 1992b). Under the conditions of the study, *o*-cresol

was considered to be not clastogenic in the *in vivo* micronucleus test.

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

Additional References: Florin (1980); Nestmann (1980); Haworth (1983); Douglas (1980); Jansson (1986); Cheng (1984); Ohshima (1989); Massey (1994); Levan (1948); Witt (2000); Kubo (2002); Li (2005); US EPA, 1981; US EPA, 1988b; US EPA, 1989; US EPA, 1988d.

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

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on *o*-cresol or any read-across materials. The total systemic exposure to *o*-cresol is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on *o*-cresol. A subchronic neurotoxicity study (RIFM, 1986) is considered weight of evidence only, due to the lack of data available on liver and kidney effects. Groups of 10 Sprague Dawley rats/sex/dose (20 Sprague Dawley rats/sex/dose for the control, 0 mg/kg/day) were administered *o*-cresol via gavage (vehicle: corn oil) at doses of 0, 50, 175, 450, or 600 mg/kg/day for 13 weeks (once daily). Observations included mortality, body weight, feed consumption, clinical signs, an observational battery of neurobehavioral tests, gross necropsy, neuropathology on all rats, and histopathology on select organs from rats found dead during the study. Mortality was observed at 450 mg/kg/day (10%) and 600 mg/kg/day (50%) and was greatest during the first few weeks of the study. Gross and histopathologic examinations revealed that the majority of the deaths were treatment-related, either due to the direct effects of *o*-cresol, aspiration or inhalation of *o*-cresol, or pulmonary edema. At 450 and 600 mg/kg/day, significantly decreased feed consumption was observed in males during the beginning of the study. Clinical signs such as salivation, myotonus, tremors, urine-wet abdomen, hypoactivity, rapid respiration, myoclonus, low body posture, and labored respiration occurred in all dose groups and were dose-dependent. An increase in urination was observed in females at 600 mg/kg/day but was found to be related to the general health of the animal rather than an overt behavioral change.

There are no repeated dose toxicity data on o-cresol or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.39 μg/kg/day) is below the TTC for o-cresol (30 μg/kg/day; Kroes, 2007).

Additional References: None.

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

11.1.3. Skin depigmentation

For applications on areas of skin, there is no concern for depigmentation at current use levels.

11.1.3.1. Risk assessment. Five female CBA/J agouti mice per group were exposed to *o*-, *m*-, and *p*-cresol at concentrations of 0.5% in acetone (Shelley, 1974). The lower back hair of the animals was plucked or clipped, and each compound was applied topically 3 times/week for 6 weeks as a spray mist from a tuberculin syringe. In another instance, 30 black C57 BL/6J male mice were exposed to 0.5% (in acetone) *p*-cresol. All the animals were observed for 6 months after the administration of the last dose for changes in hair color. The study results demonstrated that *p*-cresol exposure caused patterned depigmentation in 2/5 agouti mice in both plucked and clipped groups. Patches of pigment loss were observed in C57 BL/6J mice following the application of *p*-cresol. In the C57 BL/6J mice, a local corrosive effect and depigmentation of the epidermis were also seen after repeated applications. Neither *o*- nor *m*-cresol resulted in the loss of hair pigment. The results indicate that *p*-cresol was responsible for depigmentation in both studies. Thus, based on no adverse effects seen at the only dose tested, the NOAEL for *o*-cresol and m-cresol is 0.5%. The NOAEL is adjusted by a safety factor of 10 for a maximum safe-use level of 0.05%.

Additional References: None.

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

11.1.4. Reproductive toxicity

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

11.1.4.1. Risk assessment. The developmental toxicity data on *o*-cresol are sufficient for the developmental toxicity endpoint. In a developmental toxicity study, 14 pregnant New Zealand white rabbits/sex/dose were administered *o*-cresol via gavage at doses of 0 (vehicle: corn oil), 5, 50, or 100 mg/kg/day on days 6–18 of gestation. All females were euthanized on day 29 of gestation for Caesarean section. Observations included mortality, clinical signs, body weight, and feed consumption. The gravid uterus, ovaries (including corpora lutea), cervix, vagina, and abdominal and thoracic organs and cavities were examined grossly. Ovarian corpora lutea of pregnancy were counted. Maternal liver and uterine weights were determined. The uterus was removed from the abdominal cavity and dissected longitudinally to expose the contents and examined for signs of hemorrhage. All live and dead fetuses and resorption sites (early and late) were noted and recorded. All live fetuses were immediately euthanized, weighed, sexed internally, and examined for external malformations (including cleft palate and variations) and thoracic and abdominal visceral abnormalities. One-half of the fetuses in each litter were examined for craniofacial structures by sectioning methods. All fetuses in each litter (50% intact and 50% decapitated) were eviscerated, air-dried, and then processed for skeletal malformations and variations. Mortality was seen in 2 females at 50 mg/kg/day and 5 females at 100 mg/kg/day. Clinical signs of toxicity in these groups were ocular discharge, hypoactivity, gasping, cyanosis, and audible labored and rapid respiration. Based on no developmental toxicity at any dose level, the developmental toxicity NOAEL was determined to be 100 mg/kg/day (US EPA, 1988c).

Therefore, the MOE for developmental toxicity is equal to the NOEL in mg/kg/day divided by the total systemic exposure, 100/0.00039, or 256410.

The fertility data on *o*-cresol are sufficient for the reproductive toxicity endpoint. In a reproductive toxicity study following the Continuous Breeding Protocol, groups of 20 CD-1 Swiss mice/sex/dose were administered *o*-cresol via the diet at concentrations of 0%, 0.05%, 0.2%, or 0.5% (equivalent to 0, 66, 263, and 660 mg/kg/day) through 1 week of pre-cohabitation and 14 weeks of cohabitation. Mice were then housed singly for an additional 6-week holding period. Any litters born during the holding period were considered the F1 generation. F1 generation mice produced from the 0% and 0.5% groups were fed the same diets as their parents (equivalent to 0 and 773 mg/kg/day) and were mated at sexual maturity to produce the F2 generation. Observations included mortality, body weight, feed consumption, water consumption, mating, fertility, reproductive performance, cumulative days to litter, estrous cycling, organ weights, sperm analyses, histopathology, pup survival, and body weights. There were no adverse effects on F0 body weight, food or water consumption, gross examinations, histopathological examinations, or measures of reproductive competence, including initial fertility, the number of litters per pair, live litter size, proposition of pups born alive, or adjusted live pup weight. The only organ weight change was a decrease in absolute kidney weight in F0 females at the high dose. Cumulative days to litter was slightly increased in all F0 treatment groups but was not dose-dependent. There were no adverse effects on F1 preweaning growth or survival, food or water consumption, clinical signs, organ weights, histopathology, or

reproductive performance. Body weight was slightly reduced in F1 females at the high dose. Based on no adverse effects on reproductive performance seen up to the highest dose in the F0 or F1 generation, the fertility NOAEL for this study was considered to be 0.5% or 773 mg/kg/day (NTP, 1992a).

Therefore, the MOE for reproductive toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 773/0.00039, or 1982051.

In addition, the total systemic exposure to *o*-cresol (0.39 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: None.

Literature Search and Risk Assessment Completed On: 04/08/20.

11.1.5. Skin sensitization

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

11.1.5.1. Risk assessment. Limited skin sensitization studies are available for *o*-cresol. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly, while its autoxidation 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 *o*-cresol was found to be inconclusive. In a human maximization test, no skin sensitization reactions were reported (RIFM, 1980). 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. Table 1 provides the maximum acceptable concentrations for *o*-cresol that present no appreciable risk for skin sensitization based on the 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: 04/06/20.

11.1.6. Phototoxicity/photoallergenicity

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

11.1.6.1. Risk assessment. There are no phototoxicity studies available for *o*-cresol in experimental models. UV/Vis absorption spectra indicate minor absorption 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 significant absorbance in the critical range, *o*-cresol does not present a concern for phototoxicity or photoallergenicity.

11.1.6.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. 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: 04/06/20.

11.1.7. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data.

Table 1
Maximum acceptable concentrations for *o*-cresol that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	5.6×10^{-5}%
2	Products applied to the axillae	0.0015%	1.6×10^{-5}%
3	Products applied to the face using fingertips	0.029%	3.9×10^{-8}%
4	Fine fragrance products	0.027%	1.1×10^{-4}%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	4.2×10^{-6}%
6	Products with oral and lip exposure	0.016%	0.0150%
7	Products applied to the hair with some hand contact	0.056%	4.2×10^{-7}%
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	2.5×10^{-6}%
10	Household care products with mostly hand contact	0.19%	4.6×10^{-4}%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	5.5×10^{-4}%

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

The exposure level for *o*-cresol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.7.1. Risk assessment. There are insufficient inhalation data available on *o*-cresol. Based on the Creme RIFM Model, the inhalation exposure is 0.0000085 mg/day. This exposure is 164706 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); US EPA, 1978; Campbell (1941); Hagmar, 1988a; Hagmar, 1988b; Pero (1988); Chin (1941); Bieniek (1997); US EPA, 1949; US EPA, 1978; Campbell (1941); Bieniek (1994); Chin (1941); Uzhdavini (1974); Uzhdaini (1972); US EPA, 1978; Campbell (1941); ECHA, 2011a; ECHA, 2011b; ECHA, 2011c.

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 *o*-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, *o*-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 *o*-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 VoU (2015), *o*-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.

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

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 86% was observed after 20 days.

The ready biodegradability of the test material was evaluated using the modified MITI test (I) according to the OECD 301C 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 302B guideline. Biodegradation of 100% (DOC removal) was observed after 7 days.

The inherent biodegradability of the test material was evaluated using the Zahn-Wellens test, according to the OECD 302B guideline. Biodegradation of 95% (COD removal) was observed after 5 days.

The acute toxicity of *o*-cresol to fish (*Salmo trutta*) was determined with a static bioassay on several freshwater species. The 96-h LC50 value based on nominal concentration was reported to be 6.2 mg/L.

The acute toxicity of *o*-cresol to *Daphnia pulex* was determined in a static immobilization test after an exposure period of 48 h. The test was carried out in accordance with a Dutch standard method similar to the OECD 202 guideline. The lowest nominal EC50 value based on nominal concentration was reported to be 9.6 mg/L.

An algae growth inhibition test was conducted according to NEN-6506 (1980) guidelines under static conditions. The 96-h EC50 value of 100 mg/L based on nominal concentrations was reported for *o*-cresol.

11.2.3.3.1. Risk assessment refinement. Since *o*-cresol has passed the screening criteria (Tier 1), measured REACH data 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*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	151.8			1000000	0.1518	

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	<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 0.1518 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

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

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 09/30/20.

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. 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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