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Short Review

RIFM fragrance ingredient safety assessment, *p*-tolyl acetate, CAS Registry Number 140-39-6

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ABSTRACT

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

p-Tolyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl *p*-tolyl carbonate (CAS # 22719-81-9) show that *p*-tolyl acetate is not expected to be genotoxic. Data on read-across materials *p*-cresol (CAS # 106-44-5) and acetic acid (CAS # 64-19-7) provide a calculated MOE > 100 for the repeated dose and reproductive toxicity endpoints. The skin sensitization endpoint was completed using DST for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; *p*-tolyl acetate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to *p*-tolyl acetate is below the TTC (1.4 mg/day).The environmental endpoints were evaluated; *p*-tolyl acetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

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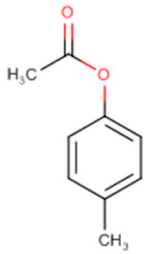
Name: *p*-Tolyl acetate
CAS Registry Number: 140-39-6



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
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
QRA - Quantitative Risk Assessment
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.

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

p-Tolyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl *p*-tolyl carbonate (CAS # 22719-81-9) show that *p*-tolyl acetate is not expected to be genotoxic. Data on read-across materials *p*-cresol (CAS # 106-44-5) and acetic acid (CAS # 64-19-7) provide a calculated MOE > 100 for the repeated dose and reproductive toxicity endpoints. The skin sensitization endpoint was completed using DST for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; *p*-tolyl acetate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to *p*-tolyl acetate is below the TTC (1.4 mg/day).The environmental endpoints were evaluated; *p*-tolyl acetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (Bhalli, 2014; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day. (NTP, 2008)
Reproductive Toxicity: Developmental toxicity: NOAEL = 100 mg/kg/day. Fertility: NOAEL = 450 mg/kg/day. (EPA, 1988a; EPA, 1989)
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.
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: Screening-level: 2.9 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 11.4 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 152.8 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: 152.8 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.1528 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name**: *p*-Tolyl acetate
2. **CAS Registry Number:** 140-39-6
3. **Synonyms:** Acetic acid, 4-methylphenyl ester; Acetyl *p*-cresol; *p*-Cresyl acetate; *p*-Cresylic acetate; *p*-Tolyl ethanoate; ｐ - アセトキシトルエン; アルキル（Ｃ＝１～７）カルボン酸クレジル; 4-Methylphenyl acetate; *p*-Tolyl acetate
4. **Molecular Formula:** $C_9H_{10}O_2$
5. **Molecular Weight:** 150.17
6. **RIFM Number:** 354
7. **Stereochemistry:** No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 212 °C (FMA Database), 215.56 °C (EPI Suite)
2. **Flash Point:** 91 °C (GHS), 195 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.14 (EPI Suite)
4. **Melting Point**: 5.75 °C (EPI Suite)
5. **Water Solubility:** 1195 mg/L (EPI Suite)
6. **Specific Gravity:** 1.046–1.052 (FMA Database), 1.044–1.050 (FMA Database)
7. **Vapor Pressure:** 0.128 mm Hg @ 20 °C (EPI Suite v4.0), 0.192 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A clear, colorless to pale yellow liquid with a strong floral character

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0014% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.0000035 mg/kg/day or 0.00025 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.000046 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
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2. Analogs Selected:
   a. **Genotoxicity:** Ethyl *p*-tolyl carbonate (CAS #: 22719-81-9)
   b. **Repeated Dose Toxicity:** *p*-Cresol (CAS # 106-44-5) and acetic acid (CAS # 64-19-7)
   c. **Reproductive Toxicity:** *p*-Cresol (CAS # 106-44-5) and acetic acid (CAS # 64-19-7)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

6.1. Additional References

None.

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

p-Tolyl acetate is reported to occur in the following foods by the VCF*:

Cocoa category

*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.

8. IFRA standard

None.

9. REACH dossier

Available; accessed 11/15/18 (ECHA, 2017).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. *p*-Tolyl acetate was assessed in the BlueScreen assay and found positive for cytotoxicity with metabolic activation (positive: < 80% relative cell density) and positive for genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of *p*-tolyl acetate; however, read-across can be made to ethyl *p*-tolyl carbonate (CAS # 22719-81-9; see Section V). The mutagenic activity of ethyl *p*-tolyl carbonate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with ethyl *p*-tolyl carbonate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (Bhalli and Phil, 2014). Under the conditions of the study, ethyl *p*-tolyl carbonate was not mutagenic in the Ames test, and this can be extended to *p*-tolyl acetate.

The clastogenic activity of *p*-tolyl acetate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with *p*-tolyl acetate in DMSO at concentrations up to 1500 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. *p*-Tolyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2014). Under the conditions of the study, *p*-tolyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: RIFM, 2015.

Literature Search and Risk Assessment Completed On: 01/03/18.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for *p*-tolyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. *p*-Tolyl acetate is expected to hydrolyze to *p*-cresol and acetic acid. Thus, toxicity data available on *p*-cresol (CAS # 106-44-5; see Section V) and acetic acid (CAS # 64-19-7; see Section V) are used for the safety assessment of *p*-tolyl acetate.

Toxicity data on *p*-cresol have been extensively reviewed by several organizations, among which Health Canada provides the most recent review (Health Canada Assessment, 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-CoRAP evaluation suggests that the available data do not present a carcinogenic hazard to humans (NTP, 2008; ECHA-CoRAP evaluation of p-cresol).

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 body-weight gains were significantly reduced among high-dose group animals. Relative kidney weights were increases 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) while 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 (https://echa.europa.eu/registration-dossier/-/registered-dossier/15980/7/6/2 ECHA, 2011).

In addition to systemic toxicity, *p*-cresol (0.5%) 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 review, 1994).

Since the available systemic toxicity data on *p*-cresol allows for determination of a NOAEL for the repeated dose toxicity endpoint and the fact that skin depigmentation is a local effect, a NOAEL of 50 mg/kg/day was determined from the 90-day gavage study in rats. The hydrolysis product acetic acid has been reviewed by several agencies. The US Food and Drug Administration (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=184.1005 FDA, 21CFR184.1005, Revised as of April 1, 2018; accessed on 12/18/2018) has granted acetic acid a generally recognized as safe (GRAS) status. JECFA (2006; accessed on 12/18/2018) also evaluated acetic acid and stated that for acetic acid it is not necessary to indicate acceptable daily intakes for humans. The European Food Safety Authority (EFSA), reviewed the data on acetic acid (Scientific Opinion on the safety and efficacy of acetic acid, sodium diacetate and calcium acetate as preservatives for feed for all animal species, 2012; accessed on 12/18/2018). They stated that there is now an application for the reauthorization of acetic acid and these salts as preservatives in feed and for the new use of acetic acid as a preservative in water for drinking. They may be used alone or in combination with other organic acids typically in a concentration of 200–2500 mg acetate/kg complete feeding stuffs. The Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) provides a comprehensive review of the toxicity data on acetic acid as a part of their human health Tier II assessment for acetic acid (2016; accessed on 12/18/2018). They state that acetates are normal components in human and animal diets. They are produced in small (molar) quantities daily in the gastrointestinal tract, where they are rapidly and completely metabolized. Acetate is produced as a major intermediate in normal metabolic processes. Various isotope experiments have shown that the different carbon atoms of acetic acid are used in glycogen formation as intermediates of carbohydrates and fatty acid synthesis as well as in cholesterol synthesis. In addition, acetic acid also participates in the acetylation of amines and formation of proteins of plasma, the liver, kidney, gut mucosa, muscle, and brain. Acetic acid is absorbed from the gastrointestinal tract and through the lungs. Following absorption, acetic acid is almost completely metabolized by most tissues and may give rise to the production of

ketone bodies as intermediates. The level of the acetate ion in humans has been estimated at about 50–60 μmoL/L (3.0–3.6 mg/L) in plasma and 116 μmoL/L (7 mg/L) in cerebrospinal fluid. Daily turnover of the acetate ion in humans is estimated at about 7.5 μmoL/kg/min representing about 45 g/day. Based on the treatment-related effects reported in limited repeated dose toxicity studies, acetic acid is not considered to cause serious damage to health from repeated oral exposure. The effects observed in some cases could have been only due to the corrosive activity of acetic acid. Results from repeated oral, inhalation, and dermal exposure of humans to acetic acid have been reported with effects on the gastrointestinal tract, digestive disorders including heartburn and constipation, chronic inflammation of the respiratory tract, pharyngitis, catarrhal bronchitis, darkening of skin, skin dermatitis, and erosion of the exposed front teeth enamel. In addition, skin on the palms of the hands can become dry, cracked, and hyperkeratotic. These observed effects were not associated with any systemic findings, suggesting the effects observed could be due to its corrosive activity. Based on the limited data available, acetic acid is not likely to be a carcinogen. Based on the available data, acetic acid does not show specific reproductive or developmental toxicity. Thus, acetic acid does not pose systemic (repeated dose) or developmental and reproductive toxicity to human health when used in fragrances.

The NOAEL of 50 mg/kg/day from *p*-cresol was considered for the safety assessment of *p*-tolyl acetate.

Therefore, the *p*-tolyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the *p*-cresol NOAEL in mg/kg/day by the total systemic exposure for *p*-tolyl acetate, 50/0.000046 or 1086956.

In addition, the total systemic exposure to *p*-tolyl acetate (0.046 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/10/19.

10.1.3. Reproductive toxicity

The MOE for *p*-tolyl acetate is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on *p*-tolyl acetate. *p*-Tolyl acetate is expected to hydrolyze to *p*-cresol (CAS # 106-44-5; see Section V) and acetic acid (CAS # 64-19-7; see Section V). Based on the available data on acetic acid (EFSA, 2012; NICNAS, 2016; US FDA, 2018), acetic acid does not show specific developmental toxicity or fertility effects. Thus, acetic acid does not pose any systemic (repeated dose), developmental toxicity, or fertility effects to human health when used in fragrances.

There are sufficient developmental toxicity data on read-across material *p*-cresol (CAS # 106-44-5; see Section V). 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 GD 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; 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*-tolyl acetate 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*-tolyl acetate, 100/0.000046 or 2173913.**

There are sufficient fertility data on read-across material *p*-cresol (CAS # 106-44-5; see Section V). 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. 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/day. 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 $\geq$175 mg/kg/day, increased mortality, and reduced bodyweight gain at 450 mg/kg/day. The NOAEL for effects of fertility was considered to be 450 mg/kg/day, the highest dose tested (EPA, 1989; sub-reference 11/13). **Therefore, the *p*-tolyl acetate 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*-tolyl acetate, 450/0.000046 or 9782609.**

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; https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/15980/7/9/3 ECHA, 2011 (accessed 12/21/18)

In addition, the total systemic exposure to *p*-tolyl acetate (0.046 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

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

Literature Search and Risk Assessment Completed On: 01/04/19.

10.1.4. Skin sensitization

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

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In 2 guinea pig open epicutaneous tests, no skin sensitization reactions were observed (Klecak, 1985). In a human maximization study with 24 human volunteers, 1 subject showed skin reactions indicative of skin sensitization in response to 4% or 2760 μg/cm^2 *p*-tolyl acetate (RIFM, 1975). In another human maximization study with 25 human volunteers, no skin sensitization reactions were observed when 4% or 2760 μg/cm^2 *p*-tolyl acetate was used (RIFM, 1972). Acting conservatively due to the insufficient data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). 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 *p*-tolyl acetate 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: 11/30/18.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for p-tolyl acetate in experimental models. UV/Vis absorption spectra

Table 1
Maximum acceptable concentrations for *p*-tolyl acetate 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%	2.1×10^{-5}%
2	Products applied to the axillae	0.0015%	4.0×10^{-4}%
3	Products applied to the face using fingertips	0.029%	5.2×10^{-5}%
4	Fine fragrance products	0.027%	0.0023%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	1.3×10^{-4}%
6	Products with oral and lip exposure	0.016%	6.0×10^{-6}%
7	Products applied to the hair with some hand contact	0.056%	2.0×10^{-5}%
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	4.9×10^{-4}%
10	Household care products with mostly hand contact	0.19%	0.0010%
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	0.012%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, p-tolyl acetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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 $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/20/18.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on p-tolyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.00025 mg/day. This exposure is 5600 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/12/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of *p*-tolyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, *p*-tolyl acetate 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*-tolyl acetate 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥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).

10.2.2. Risk assessment. Based on the current Volume of Use (2015), *p*-tolyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. p-Tolyl acetate has been pre-registered for REACH with no additional data at this time.

10.2.3. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>152.8</u>			1000000	0.1528	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.1	2.1
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 additional assessment is necessary.

The RIFM PNEC is 0.1528 μg/L. The revised PEC/PNECs for EU and NA 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 VoU.

Literature Search and Risk Assessment Completed On: 12/10/18.

11. 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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 05/31/19.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.111002.

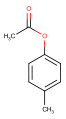
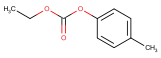
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	*p*-Tolyl acetate	Ethyl *p*-tolyl carbonate	Acetic acid	*p*-Cresol
CAS No.	140-39-6	22719-81-9	64-19-7	106-44-5
Structure				
Similarity (Tanimoto Score)		0.61	0.14	0.52
Read-across Endpoint		• Genotoxicity	• Repeated Dose • Reproductive Toxicity	• Repeated Dose • Reproductive Toxicity
Molecular Formula	$C_9H_{10}O_2$	$C_{10}H_{12}O_3$	$C_2H_4O_2$	C_7H_8O
Molecular Weight	150.17	180.20	60.05	108.14
Melting Point (°C, EPI Suite)	5.75	−12.11	16.635	201.9
Boiling Point (°C, EPI Suite)	212.5	265.93	117.9	201.9
Vapor Pressure (Pa @ 25°C, EPI Suite)	25.6	1.54	2.09E+003	1.47E+001
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.11	2.49	−0.17	1.94

Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1195	411.6	2.09E + 003	2.15e + 004
J_{max} (μg/cm^2/h, SAM)	66.45	24.17	6283.04	1165.9
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.24E + 000	3.40E + 001	1e + 006	1.01E-001
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• AN2|AN2 ≫ Schiff base formation after aldehyde release|AN2 ≫ Schiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters |SN2|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2|SN2 ≫ Nucleophilic substitution at sp3 carbon atom ≫ Specific Acetate Esters	• No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found		
Carcinogenicity (ISS)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (moderate reliability)		
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found		
Oncologic Classification	• Not classified	• Not classified		
Repeated Dose Toxicity				
Repeated dose (HESS)	• Acetaminophen (Hepatotoxicity) Alert|Acetaminophen (Renal toxicity) Alert|Phenacetin (Hepatotoxicity) Alert|Phenacetin (Renal toxicity) Alert		• Acetamide (Renal Toxicity) Alert|Carboxylic acids (Hepatotoxicity) No rank	• Acetaminophen (Hepatotoxicity) Alert|Acetaminophen (Renal toxicity) Alert|*p*-Alkylphenols (Hepatotoxicity) Rank A|Phenols (Mucous membrane irritation) Rank C|Toluene (Renal toxicity) Alert
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group		• Non-binder, non-cyclic structure	• Weak binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (moderate reliability)		• Toxicant (low reliability)	• Non-toxicant (good reliability)
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 1	• No metabolites	• See Supplemental Data 1

Summary

There are insufficient toxicity data on *p*-tolyl acetate (CAS # 140-39-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, ethyl *p*-tolyl carbonate (CAS # 22719-81-9), acetic acid (CAS # 64-19-7), and *p*-cresol (CAS # 106-44-5) were identified as read-across analogs with sufficient data for toxicological evaluation.

13. Conclusions

- Ethyl *p*-tolyl carbonate (CAS # 22719-81-9) was used as a read-across analog for the target material *p*-tolyl acetate (CAS # 140-39-6) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of aromatic esters.
  - o The target material and the read-across analog share a *p*-tolyl alcohol group.
  - o The key difference between the target material and the read-across analog is that while the acid group in the target ester is an acetic acid, the acid group in the read-across ester is a carbonic acid. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material presents several DNA binding alerts according to the OASIS v1.4, QSAR Toolbox v4.2 that are specific for acetate esters. However, a literature search shows that *p*-tolyl group inhibits all the reactions associated with this alert. Consequently, the predictions are superseded by data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Read-across alcohol *p*-cresol (CAS # 106-44-5) and read-across acid acetic acid (CAS # 64-19-7) are used as read-across analogs for the target ester *p*-tolyl acetate (CAS # 140-39-6) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - o Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - o The target material has several alerts for repeated dose (HESS). These alerts are due to structural Dice similarities higher than 50% compared to acetaminophen and phenacetin molecules, which display hepatotoxicity and renal toxicity. The alert can therefore be ignored.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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