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RIFM fragrance ingredient safety assessment, *p*-tolyl octanoate, CAS Registry Number 59558-23-5

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP, 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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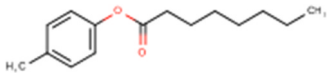

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Name: *p*-Tolyl octanoate
CAS Registry Number: 59558-23-5

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

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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

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

p-Tolyl octanoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog *p*-tolyl 3-methylbutyrate (CAS # 55066-56-3) show that *p*-tolyl octanoate is not expected to be genotoxic. Data on read-across analogs *p*-cresol (CAS # 106-44-5) and octanoic acid (CAS # 124-07-2) provide a calculated MOE >100 for the repeated dose and

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reproductive toxicity endpoints. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; *p*-tolyl octanoate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to *p*-tolyl octanoate is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). The environmental endpoints were evaluated; *p*-tolyl octanoate 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. (RIFM, 2016b; RIFM, 2016a)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day. (ECHA REACH Dossier: p-Cresol; ECHA, 2011)
Reproductive Toxicity: Developmental toxicity NOAEL = 100 mg/kg/day. Fertility NOAEL = 175 mg/kg/day. (EPA, 1988a; JECDB, 2013)
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 3.05 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 1050 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 96-h Algae EC50: 0.193 mg/L (ECOSAR; US EPA, 2012b)
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: 96-h Algae EC50: 0.193 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0193 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** *p*-Tolyl octanoate
2. **CAS Registry Number:** 59558-23-5
3. **Synonyms:** *p*-Cresyl caprylate; *p*-Cresyl octanoate; *p*-Methylphenyl octanoate; Octanoic acid, 4-methylphenyl ester; *p*-Tolyl caprylate; ｱﾙｷﾙ(C = 1～7)ｶﾙﾎﾞﾝ酸ｸﾚｼﾙ; 4-Methylphenyl octanoate; *p*-Tolyl octanoate
4. **Molecular Formula:** $C_{15}H_{22}O_2$
5. **Molecular Weight:** 234.33
6. **RIFM Number:** 618
7. **Stereochemistry:** Isomer not specified. No stereocenter present, and stereoisomers not possible.

2. Physical data

1. **Boiling Point:** 314.44 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA] Database)
3. **Log K_{OW}:** 5.3 (RIFM, 2013b), 5.08 (EPI Suite)
4. **Melting Point**: 68.43 °C (EPI Suite)
5. **Water Solubility:** 1.313 mg/L (EPI Suite)
6. **Specific Gravity:** 0.957 (FMA Database)
7. **Vapor Pressure:** 0.000185 mm Hg at 20 °C (EPI Suite v4.0), 0.000353 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** No significant absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless oily liquid

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 v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.030% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.000058 mg/kg/day or 0.0039 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.00033 mg/kg/day (RIFM, 2017)

*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 v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** *p*-Tolyl 3-methylbutyrate (CAS # 55066-56-3)
   b. **Repeated Dose Toxicity:** *p*-Cresol (CAS # 106-44-5) and octanoic acid (CAS # 124-07-2)
   c. **Reproductive Toxicity:** *p*-Cresol (CAS # 106-44-5) and octanoic acid (CAS # 124-07-2)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

Additional References:
None.

8. Natural occurrence

p-Tolyl octanoate is not reported to occur in foods by the VCF*.

*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

p-Tolyl has been pre-registered for 2010; no dossier available as of 04/16/21.

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, *p*-tolyl octanoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. *p*-Tolyl octanoate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of *p*-tolyl octanoate; however, read-across can be made to *p*-tolyl 3-methylbutyrate (CAS # 55066-56-3; see Section VI).

The mutagenic activity of *p*-tolyl 3-methylbutyrate 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, TA1538, TA102, and *Escherichia coli* strain WP2uvrA were treated with *p*-tolyl 3-methylbutyrate 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 concentration in the presence or absence of S9 (RIFM, 2016b). Under the conditions of the study, *p*-tolyl 3-methylbutyrate was not mutagenic in the Ames test, and this can be extended to *p*-tolyl octanoate.

The clastogenic activity of *p*-tolyl 3-methylbutyrate 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 3-methylbutyrate in DMSO at concentrations up to 1920 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 800 μg/mL in the presence and absence of metabolic activation. *p*-Tolyl 3-methylbutyrate did not induce binucleated cells with micronuclei in either the presence or absence of an S9 activation system (RIFM, 2016a). Under the conditions of the study, *p*-tolyl 3-methylbutyrate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to *p*-tolyl octanoate.

Based on the data available, *p*-tolyl 3-methylbutyrate does not present a concern for genotoxic potential, and this can be extended to *p*-

tolyl octanoate.

Additional References: RIFM, 2014.

Literature Search and Risk Assessment Completed On: 11/06/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on p-tolyl octanoate. Read across materials p-cresol (CAS # 106-44-5; see Section VI) and octanoic acid (CAS # 124-07-2; see Section VI) have sufficient data to support the repeated dose toxicity endpoint.

Toxicity data on p-cresol have been extensively reviewed by several organizations, among which Health Canada provides the most recent review (Health Canada, 2016). Repeated dose toxicity for p-cresol or m- and 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 were lesions in the nasal cavity and respiratory tract. Such findings have been reported from studies on p-cresol or mixed cresols from short- or long-term exposures. It was concluded that the respiratory tract lesions reported in studies with p-cresol or mixed cresols were due to local effects resulting from inhalation of p-cresol from the diet and not as a result of systemic toxicity. Although the NTP presents equivocal evidence for carcinogenicity due to p-cresol exposure, the ECHA Co-RAP evaluation suggests that the available data do not present a carcinogenic hazard to humans (NTP, 2008; ECHA, 2016).

In an OECD 408-compliant study, p-cresol was administered via gavage to groups of 30 Sprague Dawley rats/sex/dose at doses of 0 (corn oil), 50, 175, or 600 mg/kg/day for 90 days. Mortality was reported among females (3/30) in the high-dose group. Clinical signs among animals that died included tremors, convulsions, and coma prior to death. Additionally, other clinical signs reported among treated animals included lethargy, excessive salivation, tremors, convulsions, and coma. Body weight and bodyweight gains were significantly reduced among high-dose group animals. Relative kidney weights were increased among mid- and high-dose group males. High-dose group males showed an increase in relative testes weights. Relative kidney weights increased in high-dose group animals. Hematological alterations reported among mid-dose females included reductions in red blood cell count (RBC), 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 alanine aminotransferase (at interim and terminal sacrifices) and aspartate aminotransferase in high-dose females were attributed to unusually high values in 4 animals. Serum cholesterol was statistically significantly increased in high-dose females (terminal sacrifice only), whereas total protein was increased in mid- and high-dose males. Histopathological alterations included metaplasia of tracheal epithelial. The NOAEL was considered to be 50 mg/kg/day, based on increases in relative kidney weight (ECHA, 2011).

In an OECD 422 and GLP-compliant toxicity study, groups of 12 Sprague Dawley rats/sex/dose were administered octanoic acid at doses of 0 (vehicle: 0.5% methylcellulose), 62.5, 250, and 1000 mg/kg through oral gavage. All animals in the main study received the treatment material for a total of 28 days (2 weeks before mating and 2 weeks after mating). Six animals/sex were treated as recovery groups and maintained for 14 days after the end of the 28-day treatment. In females of the mating group, the treatment period was a total of 42–46 days (14 days before mating, during mating and gestation, and up to day 4 of suckling. No treatment-related mortality or clinical signs were reported during the study. In addition, no treatment-related histopathological effects, with the exception of forestomach hyperplasia, were reported. Since the effects on the forestomach have no relevance to human health, these effects were not considered to be treatment-related adverse effects. Based on the absence of adverse effects at any dose level, the NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day (JECDB, 2013).

The most conservative NOAEL of 50 mg/kg/day was derived from the OECD 408 study on p-cresol.

Therefore, the p-tolyl octanoate 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 to p-tolyl octanoate, 50/0.00033, or 151515.

In addition, the total systemic exposure to p-tolyl octanoate (0.33 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: None.

Literature Search and Risk Assessment Completed On: 07/06/21.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on *p*-tolyl octanoate. Read-across materials *p*-cresol (CAS # 106-44-5; see Section VI) and octanoic acid (CAS # 124-07-2; see Section VI) have sufficient reproductive toxicity data.

There are sufficient developmental toxicity data on *p*-cresol. In a GLP-compliant developmental toxicity study (according to TSCA health effects test guidelines for specific organ/tissue toxicity–developmental toxicity), pregnant female New Zealand white rabbits were administered *p*-cresol via oral gavage at doses of 0, 5, 50, or 100 mg/kg/day in corn oil during GDs 6–18. The treatment groups consisted of 14 animals/dose, and the control group consisted of 28 animals. All animals were euthanized on gestation day 29. The reproductive toxicity parameters (uterus, number of corpora lutea, implantation sites, resorptions, and dead/live fetuses) were assessed. All live fetuses were counted, sexed, weighed, and examined for external, skeletal, and visceral malformations. Maternal toxicity was reported at 50 and 100 mg/kg/day, which included mortality at 50 mg/kg/day (2/13; 14.3%) and 100 mg/kg/day (5/14; 35.7%) and clinical signs of toxicity (hypoactivity, gasping, cyanosis, and labored and rapid audible respiration), and ocular discharge. No adverse treatment-related effects were reported for maternal body weight, food consumption, and necropsy at any dose level. There were no treatment-related adverse effects reported for gestational parameters or on the development of fetuses, including numbers of corpora lutea, implantation sites, live and dead fetuses, sex ratio, and fetal malformations at any dose level. Embryotoxicity or teratogenicity were not observed up to the highest dose level. Therefore, the NOAEL for maternal toxicity was considered to be 5 mg/kg/day, based on mortality and clinical signs observed among the higher dose group dams. The NOAEL for developmental toxicity was considered to be 100 mg/kg/day, the highest dose tested (EPA, 1988a). Another developmental toxicity study on *p*-cresol was conducted in rats (see Table 1 below; 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.

There are sufficient developmental toxicity data on octanoic acid. An oral gavage OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted in Crl:CD(SD) rats. For the main study, groups of 12 males/dose were administered octanoic acid at doses of 0, 62.5, 250, or 1000 mg/kg/day in 0.5% methylcellulose, with half of these males assigned to the corresponding recovery groups. Groups of 10 females/dose were

Table 1
Additional developmental toxicity study in rats.

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

administered octanoic acid at doses of 0 or 1000 mg/kg/day, with half of these females assigned to the corresponding recovery groups. Additional groups of 5 females/dose were administered 62.5 or 250 mg/kg/day octanoic acid. Main-phase females were not used for mating. For the reproduction phase, additional groups of 12 female rats/dose (0, 62.5, 250, or 1000 mg/kg/day) were mated with males of the main study. In the main group, the animals were treated for 28 days, with a 14-day recovery period. In the reproduction group, the animals were dosed for 14 days premating and for 42–46 days during the mating and gestation periods and up to day 4 of lactation. No treatment-related effects were noted on body weight or food consumption in males or females of the main or recovery groups. There were no treatment-related adverse effects on the development of pups up to the highest dose tested. Thus, the NOAEL for maternal and reproductive toxicity was considered to be 1000 mg/kg/day (JECDB, 2013). Considering all the studies, the most conservative NOAEL of 100 mg/kg/day from the rabbit study for *p*-cresol was selected for the developmental toxicity endpoint. Therefore, the *p*-tolyl octanoate MOE for the developmental toxicity endpoint can be calculated by dividing the *p*-cresol NOAEL in mg/kg/day by the total systemic exposure for *p*-cresol, 100/0.00033, or 303030.

There are sufficient fertility data on *p*-cresol. A GLP-compliant, 2-generation reproductive toxicity study (according to TSCA health effects test guideline for specific organ/tissue toxicity-reproduction/ fertility effects) was conducted in Sprague Dawley rats. Groups of 25 rats/sex/dose (for both F0 and F1 generations) were administered via oral gavage *p*-cresol at doses of 0, 30, 175, or 450 mg/kg/day in corn oil. Animals were dosed for 5 days per week for 10 weeks (F0 generation) and 11 weeks (F1 generation) during the premating period. After the premating period, F0 male and female rats were dosed daily through mating for 3 weeks, females were dosed daily throughout the gestation and lactation periods for up to day 21 post-partum, and F0 males were dosed until necropsy. Groups of F1 rats were treated similarly to the parental generation to produce the F2 generation. At 450 mg/kg/day, mortality was reported for both F0 and F1 generation male (28%–36%) and female (32%–40%) animals. Treatment-related statistically significant decreases in body weight (13%) and bodyweight gains were reported primarily in F0 and F1 males at 450 mg/kg/day. A statistically significant decrease in food consumption was also noted in F0 and F1 animals at 450 mg/kg/day. Clinical signs of toxicity were reported in F0 and F1 parental rats (hypoactivity, ataxia twitches, tremors, prostration, urine stains, and audible respiration) at 450 mg/kg/day, and statistically significant increased incidences of perioral wetness were reported in both the sexes at 175 and 450 mg/kg/day. Perinasal encrustation and urogenital wetness were also noted in F0 and F1 females at 450 mg/kg/day. At 450 mg/kg/day, 3/18 F1 males that survived until the end of treatment exhibited seminiferous tubule atrophy and degeneration as well as decreased epididymal sperm. Microscopic observations of a decreased number of spermatozoa that were reported in a small number of animals failed to reveal a target organ or a mechanism of toxicity; hence, the observed effects from necropsy and histopathology of F1 animals were not considered to be treatment-related. No treatment-related findings at necropsy or histopathological findings were observed in F0 and F1 animals that survived until the end of treatment. No treatment-related adverse effects were reported on estrous cycling, mating, fertility, gestation, or sperm parameters at any dose level in both F0 and F1 generations. *p*-Cresol caused an increase in stillbirths in both the F1 and F2 generations for F1 pups at 175 mg/kg/day (but not 450 mg/kg/day) and F2 pups at 30 and 450 mg/kg/day (but not at 175 mg/kg/day). In the F2 (but not F1) group, live birth indices were reduced at 30 and 450 mg/kg/day (but not 175 mg/kg/day). There was no clear dose-dependent effect in both generations. Pup survival indices in both generations were not affected by treatment at any dose level. Therefore, the NOAEL for parental toxicity was considered to be 30 mg/kg/day, based on clinical signs of toxicity at ≥175 mg/kg/day, increased mortality, and reduced bodyweight gain at 450 mg/kg/day. Microscopic observations of a decreased number of spermatozoa that was reported in a small number of animals failed to reveal a target organ or a mechanism of toxicity. However, based on the decrease in epididymal sperm and microscopic decrease in the number of spermatozoa in F1 males, the most conservative NOAEL of 175 mg/kg/day was selected for the fertility endpoint. (EPA, 1989; sub-reference 11/13).

There are sufficient fertility data on octanoic acid. An oral gavage OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted in Crl:CD (SD) rats. For the main study, groups of 12 males/dose were administered octanoic acid at doses of 0, 62.5, 250, or 1000 mg/kg/day in 0.5% methylcellulose, with half of these males assigned to the corresponding recovery groups. Groups of 10 females/dose were administered octanoic acid at doses of 0 or 1000 mg/kg/day, with half of these females assigned to the corresponding recovery groups. Additional groups of 5 females/dose were administered 62.5 or 250 mg/kg/day octanoic acid. Main-phase females were not used for mating. For the reproduction phase, additional groups of 12 female rats/dose (0, 62.5, 250, or 1000 mg/kg/day) were mated with males of the main study. In the main group, the animals were treated for 28 days, with a 14-day recovery period. In the reproduction group, the animals were dosed for 14 days premating and for 42–46 days during the mating and gestation periods and up to day 4 of lactation. No treatment-related effects were noted on body weight or food consumption in males or females of the main or recovery groups. There were no treatment-related adverse effects on

male and female fertility or on the development of pups up to the highest dose tested. Thus, the NOAEL for maternal and reproductive toxicity was considered to be 1000 mg/kg/day (JECDB, 2013). Considering all the studies, the most conservative NOAEL of 175 mg/kg/day from the study for *p*-cresol was selected for the fertility endpoint. Therefore, the *p*-tolyl octanoate MOE for the fertility endpoint can be calculated by dividing the *p*-cresol NOAEL in mg/kg/day by the total systemic exposure for *p*-cresol, 175/0.00033, or 530303.

In addition, the total systemic exposure to *p*-tolyl octanoate (0.33 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: 11/05/20.

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for *p*-tolyl octanoate. The chemical structure of this material indicates that it is not expected to react with skin proteins. *p*-Tolyl octanoate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) (RIFM, 2020b). In a human maximization test, no skin sensitization reactions were observed at 4% or 2760 μg/cm^2 of *p*-tolyl octanoate (RIFM, 1975). 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 *p*-tolyl octanoate 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: 11/02/20.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for *p*-tolyl octanoate in experimental models. UV/Vis absorption spectra 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, 2009). Based on the lack of absorbance, *p*-tolyl octanoate 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 no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/23/20.

11.1.6. Local Respiratory Toxicity

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

Table 2
Maximum acceptable concentrations for *p*-tolyl octanoate 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%	0.0020%
3	Products applied to the face using fingertips	0.41%	2.0×10^{-4}%
4	Fine fragrance products	0.39%	0.030%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.0030%
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	4.8×10^{-4}%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0012%
10	Household care products with mostly hand contact	2.7%	0.0034%
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	0.40%

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.

11.1.6.1. Risk assessment. There are no inhalation data available on *p*-tolyl octanoate. Based on the Creme RIFM Model, the inhalation exposure is 0.0039 mg/day. This exposure is 358.97 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: None.

Literature Search and Risk Assessment Completed On: 11/05/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *p*-tolyl octanoate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the

material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, *p*-tolyl octanoate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify *p*-tolyl octanoate 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).

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

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. *p*-Tolyl octanoate has been registered for REACH with no additional information available at this time.

11.2.2. 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	North America
Log K_{ow} Used	5.3	5.3
Biodegradation Factor Used	1	1
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 0.0193 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 10/27/20.

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/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.43			1000000	0.00043	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.496	0.740	0.193	10000	0.0193	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.327	0.247	0.597			Neutral Organic SAR

- **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 04/16/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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 B. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2021.112513.

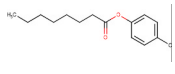
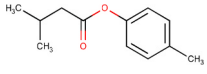
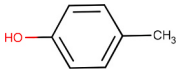
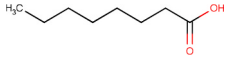
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017).

- 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 (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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 octanoate	*p*-Tolyl 3-methylbutyrate	*p*-Cresol	Octanoic acid
CAS No.	59558-23-5	55066-56-3	106-44-5	124-07-2
Structure				
Similarity (Tanimoto Score)		0.82	0.35	0.30
SMILES	CCCCCCCC(=O)Oc1ccc(C)cc1	CC(C)CC(=O)Oc1ccc(C)cc1	Cc1ccc(O)cc1	CCCCCCCC(O)=O
Endpoint		• Genotoxicity	• Repeated dose toxicity • Reproductive toxicity	• Repeated dose toxicity • Reproductive toxicity

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
Molecular Formula	$C_{15}H_{22}O_2$	$C_{12}H_{16}O_2$	C_7H_8O	$C_8H_{16}O2$
Molecular Weight	234.339	192.258	108.14	144.214
Melting Point (°C, EPI Suite)	68.43	27.83	35.50	16.30
Boiling Point (°C, EPI Suite)	314.44	258.97	201.90	239.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.71E-02	2.11E+00	1.47E+01	4.95E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.31E+00	4.57E+01	2.15E+04	7.89E+02
Log K_{OW}	5.08	3.54	1.94	3.05
J_{max} (μg/cm^2/h, SAM)	0.17	3.26	1165.91	77.74
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.97E+01	1.69E+01	1.01E-01	9.04E-02
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found		
Carcinogenicity (ISS)	No alert found	No alert found		
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)	Phenacetin (Hepatotoxicity) Alert|Phenacetin (Renal toxicity) Alert|Tolbutamide (Hepatotoxicity) Alert		Acetaminophen (Hepatotoxicity) Alert| Acetaminophen (Renal toxicity) Alert|p-Alkylphenols (Hepatotoxicity) Rank A| Phenols (Mucous membrane irritation) Rank C|Toluene (Renal toxicity) Alert	Carboxylic acids (Hepatotoxicity) No rank
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group		Weak binder, OH group	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		Non-toxicant (good reliability)	Non-toxicant (low reliability)
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on *p*-tolyl octanoate (CAS # 59558-23-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism predictions, physical–chemical properties, and expert judgment, *p*-tolyl 3-methylbutyrate (CAS # 55066-56-3), *p*-cresol (CAS # 106-44-5), and octanoic acid (CAS # 124-07-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target material *p*-tolyl octanoate (CAS # 59558-23-5) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to *p*-cresol (CAS # 106-44-5) and octanoic acid (CAS # 124-07-2) in the first step with 95% probability. Hence, *p*-cresol (CAS # 106-44-5) and octanoic acid (CAS # 124-07-2) can be used as read-across analogs for the target material. The read-across analogs were in domain for the *in vivo* and *in vitro* rat S9 simulator (OASIS TIMES v2.27.19).

Conclusions

- *p*-Tolyl 3-methylbutyrate (CAS # 55066-56-3) was used as a read-across analog for the target material p–Tolyl octanoate (CAS # 59558-23-5) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of cresyl esters.
  - o The key difference between the target material and the read-across analog is that the target material is an ester of octanoic acid, whereas the read-across analog is an ester of 3-methyl butyric acid. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - o The 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 a comparison of their toxicological properties.

- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- There are no *in silico* alerts for the target material and the read-across analog. *In silico* alerts are consistent with data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- 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 octanoic acid (CAS # 124-07-2) were used as read-across analogs for the target ester *p*-tolyl octanoate (CAS # 59558-23-5) for the repeated dose toxicity and reproductive toxicity endpoints.
  - 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.
  - The read-across materials are major metabolites of the target material.
  - Structural differences between the target material and the read-across analogs are mitigated by the fact that the target material could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target material is expected to be similar to that of its metabolites.
  - 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.
  - 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.
  - The target material and the read-across analogs have an acetomenphen/phenacetin-related hepatotoxicity alert from HESS. The data on the read-across analogs confirm that they have an adequate MOE at the current level of use. Therefore, based on the metabolism of the target material, structural similarities between the target material and read-across analogs, and the data on the read-across analogs, the *in silico* alerts are superseded.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

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