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Short Review

RIFM fragrance ingredient safety assessment, *p*-tolyl isobutyrate, CAS Registry Number 103-93-5

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ABSTRACT

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

p-Tolyl isobutyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs ethyl *p*-tolyl carbonate (CAS # 22,719-81-9) and *p*-tolyl acetate (CAS # 140-39-6) show that *p*-tolyl isobutyrate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to *p*-tolyl isobutyrate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 µg/cm²); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; *p*-tolyl isobutyrate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *p*-tolyl isobutyrate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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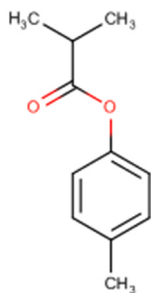
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Version: 102,820. This version replaces any previous versions.

Name: *p*-Tolyl isobutyrate

CAS Registry Number: 103-93-5



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
- Crema RIFM Model** - The Crema RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
- DEREK** - Derek Nexus is an *in silico* tool used to identify structural alerts
- DRF** - Dose Range Finding
- DST** - Dermal Sensitization Threshold
- ECHA** - European Chemicals Agency
- ECOSAR** - Ecological Structure-Activity Relationships Predictive Model
- EU** - Europe/European Union
- GLP** - Good Laboratory Practice
- IFRA** - The International Fragrance Association
- LOEL** - Lowest Observable Effect Level
- MOE** - Margin of Exposure
- MPPD** - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
- NA** - North America
- NESIL** - No Expected Sensitization Induction Level
- NOAEC** - No Observed Adverse Effect Concentration
- NOAEL** - No Observed Adverse Effect Level
- NOEC** - No Observed Effect Concentration
- NOEL** - No Observed Effect Level
- OECD** - Organisation for Economic Co-operation and Development
- OECD TG** - Organisation for Economic Co-operation and Development Testing Guidelines
- PBT** - Persistent, Bioaccumulative, and Toxic
- PEC/PNEC** - Predicted Environmental Concentration/Predicted No Effect Concentration
- Perfumery** - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use, but do not include occupational exposures.
- QRA** - Quantitative Risk Assessment
- QSAR** - Quantitative Structure-Activity Relationship
- REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
- RfD** - Reference Dose
- RIFM** - Research Institute for Fragrance Materials
- RQ** - Risk Quotient
- Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
- TTC** - Threshold of Toxicological Concern
- UV/Vis spectra** - Ultraviolet/Visible spectra
- VCF** - Volatile Compounds in Food
- VoU** - Volume of Use
- vPvB** - (very) Persistent, (very) Bioaccumulative
- WoE** - Weight of Evidence
- The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.**

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

p-Tolyl isobutyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs ethyl *p*-tolyl carbonate (CAS # 22,719-81-9) and *p*-tolyl acetate (CAS # 140-39-6) show that *p*-tolyl isobutyrate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to *p*-tolyl isobutyrate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 $\mu\text{g}/\text{cm}^2$); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; *p*-tolyl isobutyrate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *p*-tolyl isobutyrate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are < 1 .

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (Bhalli, 2014; RIFM, 2014b)

Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.

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(continued)

Reproductive Toxicity: No NOAEL available. Exposure is below TTC.**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:**

Critical Measured Value: 83% (OECD 301F) (RIFM, 2012)

Bioaccumulation:

Screening-level: 47.49 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 29.34 mg/L (RIFM Framework; Salvito, 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

	(mg/L)	(<i>Daphnia</i>) (mg/L)	(Algae) (mg/L)			
RIFM Framework Screening-level (Tier 1)	29.34			1000000	0.02934	

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito, 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 29.34 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.02934 µg/L

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

1. Identification

- Chemical Name:** *p*-Tolyl isobutyrate
- CAS Registry Number:** 103-93-5
- Synonyms:** *p*-Cresyl isobutyrate; *p*-methylphenyl isobutyrate; *p*-methylphenyl 2-methylpropanoate; propanoic acid, 2-methyl-, 4-methylphenyl ester; *p*-tolyl 2-methylpropanoate; アルキル(C = 1~7)カルボン酸クレシル; 4-Methylphenyl 2-methylpropanoate; *p*-tolyl isobutyrate
- Molecular Formula:** C₁₁H₁₄O₂
- Molecular Weight:** 178.23
- RIFM Number:** 499
- Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

- Boiling Point:** 241.5 °C (EPI Suite)
- Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA])
- Log K_{ow}:** log Pow = 3.1 (RIFM, 2013b), 3.05 (EPI Suite)
- Melting Point:** 17.09 °C (EPI Suite)
- Water Solubility:** 140.7 mg/L (EPI Suite)
- Specific Gravity:** 0.994 (FMA)
- Vapor Pressure:** 0.0274 mm Hg at 20 °C (EPI Suite v4.0), 0.03 mm Hg at 20 °C (FMA), 0.0428 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ · cm⁻¹)

9. **Appearance/Organoleptic:** Essential Oil Association Spec. no. 232: A colorless liquid which has a pronounced Lily-Narcissus-like odor, somewhat pungent and intense, but in proper dilution, pleasant

3. Volume of use (worldwide band)

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

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

- 95th Percentile Concentration in Hydroalcohols:** 0.0021% (RIFM, 2017)
- Inhalation Exposure*:** 0.000012 mg/kg/day or 0.00084 mg/day (RIFM, 2017)
- Total Systemic Exposure**:** 0.00013 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,

Table 1Maximum acceptable concentrations for *p*-tolyl isobutyrate 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%	$3.0 \times 10^{-6}\%$
2	Products applied to the axillae	0.0015%	0.0012%
3	Products applied to the face using fingertips	0.029%	$5.2 \times 10^{-5}\%$
4	Fine fragrance products	0.027%	0.0021%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	0.0011%
6	Products with oral and lip exposure	0.016%	NRU ^b
7	Products applied to the hair with some hand contact	0.056%	$7.5 \times 10^{-5}\%$
8	Products with significant ano-genital exposure	0.0029%	No Data ^c
9	Products with body and hand exposure, primarily rinse-off	0.054%	$2.2 \times 10^{-4}\%$
10	Household care products with mostly hand contact	0.19%	0.0031%
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	0.05%

Note: ^aFor a description of the categories, refer to the IFRA/RIFM Information Booklet.^bNo reported use.^cFragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

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 v3.2
I	I	I

2. Analogs Selected:

- a. **Genotoxicity:** Ethyl *p*-tolyl carbonate (CAS # 22,719-81-9); *p*-tolyl acetate (CAS # 140-39-6)
 - b. **Repeated Dose Toxicity:** None
 - c. **Reproductive Toxicity:** None
 - d. **Skin Sensitization:** None
 - e. **Phototoxicity/Photoallergenicity:** None
 - f. **Local Respiratory Toxicity:** None
 - g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

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

p-Tolyl isobutyrate 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

No dossier available as of 10/28/20.

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 isobutyrate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of *p*-tolyl isobutyrate; however, read-across can be made to ethyl *p*-tolyl carbonate (CAS # 22,719-81-9; see Section VI).

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 concentration in the presence or absence of S9 (Bhalli, 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 isobutyrate.

There are no studies assessing the clastogenic activity of *p*-tolyl isobutyrate; however, read-across can be made to *p*-tolyl acetate (CAS # 140-39-6; see Section VI).

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 dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1250 µg/mL in the presence and absence of metabolic activation. *p*-Tolyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic level concentration in either the presence or absence of an S9 activation system

(RIFM, 2014b). Under the conditions of the study, *p*-tolyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to *p*-tolyl isobutyrate.

Additional References: RIFM, 2013c; RIFM, 2013a; RIFM, 2014a; RIFM, 2015.

Literature Search and Risk Assessment Completed On: 02/19/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on *p*-tolyl isobutyrate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.13 µg/kg/day) is below the TTC for *p*-tolyl isobutyrate (30 µg/kg/day; Kroes, 2007) for a Cramer Class I material.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/12/20.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on *p*-tolyl isobutyrate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.13 µg/kg/day) is below the TTC for *p*-tolyl isobutyrate (30 µg/kg/day; Kroes, 2007; Laufersweiler, 2012) for a Cramer Class I material.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/12/20.

11.1.4. Skin sensitization

Based on existing data and the application of DST, *p*-tolyl isobutyrate 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 isobutyrate. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1974). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 µg/cm² (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for *p*-tolyl isobutyrate 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: 02/24/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *p*-tolyl isobutyrate 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 isobutyrate 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 isobutyrate 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: 02/18/20.

11.1.6. Local respiratory toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on *p*-tolyl isobutyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.00084 mg/day. This exposure is 1667 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: 02/26/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *p*-tolyl isobutyrate 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 isobutyrate 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 isobutyrate 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), *p*-tolyl isobutyrate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 2012: The ready biodegradability of the test material was evaluated following the OECD 301F guideline using the manometric respirometry test. Biodegradation of 83% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. *p*-Tolyl isobutyrate has been pre-registered for REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ($\mu\text{g/L}$)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>29.34</u>			1,000,000	0.02934	

Exposure information and PEC calculation (following RIFM Environmental Framework: [Salvito, 2002](#)).

Exposure	Europe (EU)	North America (NA)
Log K _{ow} Used	3.05	3.05
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	<1	<1

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

The RIFM PNEC is 0.02934 $\mu\text{g/L}$. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2021.112028>.

Literature Search and Risk Assessment Completed On: 02/21/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <https://echa.europa.eu/>
- **NTP:** <https://ntp.niehs.nih.gov/>
- **OECD Toolbox:** <https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm>
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **National Library of Medicine's Toxicology Information Services:** <https://toxnet.nlm.nih.gov/>
- **IARC:** <https://monographs.iarc.fr>
- **OECD SIDS:** <https://hpcvchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/public_search_publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** <https://www.google.com>
- **ChemIDplus:** <https://chem.nlm.nih.gov/chemidplus/>

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/20.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. 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.

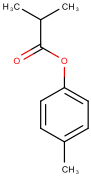
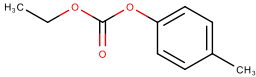
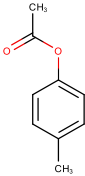
Appendix

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 Chemicals 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 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
Principal Name	<i>p</i> -Tolyl isobutyrate	Ethyl <i>p</i> -tolyl carbonate	<i>p</i> -Tolyl acetate
CAS No.	103-93-5	22,719-81-9	140-39-6
Structure			
Similarity (Tanimoto Score)		0.54	0.81
Endpoint		• Genotoxicity	• Genotoxicity
Molecular Formula	C ₁₁ H ₁₄ O ₂	C ₁₀ H ₁₂ O ₃	C ₉ H ₁₀ O ₂
Molecular Weight	178.231	180.203	150.177
Melting Point (°C, EPI Suite)	17.09	-12.11	5.75
Boiling Point (°C, EPI Suite)	241.50	265.93	212.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.71E+00	1.53E+00	2.56E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.41E+02	4.12E+02	1.20E+03
Log KOW	3.05	2.49	2.11
J_{\max} (µg/cm²/h, SAM)	7.38	9.29	31.17
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	1.28E+01	3.40E+01	7.24E+00
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	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 SN2 >> Acylation >> Specific Acetate Esters SN2 >> Nucleophilic substitution at sp ³ Carbon atom SN2 >> Nucleophilic substitution at sp ³ Carbon atom >> Specific Acetate Esters
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found
In Vitro Mutagenicity (Ames, ISS)	No alert found	No alert found	No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	No alert found	No alert found	No alert found
Oncologic Classification	Not classified	Not classified	Not classified
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

Summary

There are insufficient toxicity data on *p*-tolyl isobutyrate (CAS # 103-93-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, ethyl *p*-tolyl carbonate (CAS # 22,719-81-9) and *p*-tolyl acetate (CAS # 140-39-6) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl *p*-tolyl carbonate (CAS # 22,719-81-9) was used as a read-across analog for the target material *p*-tolyl isobutyrate (CAS # 103-93-5) for the genotoxicity endpoint.
 - o The target material and the read-across analog are structurally similar and belong to the class of esters of toluene.
 - o The target material and the read-across analog share a toluene substructure.
 - o The key difference between the target material and the read-across analog is that the target material is an ester of isobutyric acid while the read-across analog is an ester of ethyl 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 a 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 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.
- *p*-Tolyl acetate (CAS # 140-39-6) was used as a read-across analog for the target material *p*-tolyl isobutyrate (CAS # 103-93-5) for the genotoxicity endpoint.
 - o The target material and the read-across analog are structurally similar and belong to a class of tolyl esters.
 - o The target material and the read-across analog share a toluene substructure.
 - o The key difference between the target material and the read-across analog is that the target material is an ester of isobutyric acid while the read-across analog is an ester of acetic 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 a 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 read-across analog has an alert for AN2 reaction, SN2 reaction, Schiff base formation, and acylation of nucleic acids by the DNA binding model (ISS). This is specifically due to the fact that the material is an ester of acetic acid. Such esters belong to a very limited and specific scope of chemicals of different structures, since acetate esters are, in most cases, non-mutagenic. Hence, no generalized chemical mechanistic schemes associated with the positive bacterial mutagenicity (*in vitro* genotoxicity) of such acetate esters can be inferred, and different mechanisms may operate. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. The data on the read-across analog confirm that the material does not pose a concern for genetic toxicity. Therefore, based on the data and the structural similarity between the target material and the read-across analog, the alerts are superseded by the 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.

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