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Short Review

RIFM fragrance ingredient safety assessment, *p*-tolyl alcohol, CAS Registry Number 589-18-4

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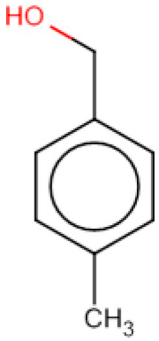

Name: *p*-Tolyl alcohol
CAS Registry Number: 589-18-4

Abbreviation/Definition List:

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2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 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
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
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 et al., 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 alcohol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog benzyl alcohol (CAS # 100-51-6) show that *p*-tolyl alcohol is not expected to be genotoxic. Data on read-across analog benzyl alcohol (CAS # 100-51-6) provide a calculated MOE > 100 for the repeated dose, developmental and local respiratory toxicity endpoints. Data from read-across analog benzyl alcohol (CAS # 100-51-6) provided *p*-tolyl alcohol a NESIL of 5900 μg/cm^2 for the skin sensitization endpoint. The reproductive toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure is below the TTC (0.03 mg/kg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; *p*-tolyl alcohol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *p*-tolyl alcohol 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.	(Zeiger et al., 1992; Hayashi et al., 1988)
Repeated Dose Toxicity: NOAEL = 100 mg/kg/day.	(National Toxicology Program, 1989)
Developmental and Reproductive Toxicity: Developmental toxicity NOAEL = 550 mg/kg/day. No reproductive toxicity NOAEL. Exposure is below the TTC.	Hardin (1986)
Skin Sensitization: NESIL = 5900 μg/cm^2.	RIFM (2005b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 1072 mg/m^3.	RIFM (2009)

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 98% (OECD 301A)	RIFM (2017c)
Bioaccumulation: Screening-level: 2.8 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 352.9 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: LC50: 352.9 mg/L RIFM Framework; Salvito (2002)
RIFM PNEC is: 0.3529 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 alcohol
2. **CAS Registry Number:** 589-18-4
3. **Synonyms:** Benzenemethanol, 4-methyl-; *p*-Methylbenzyl alcohol; 4-Methylbenzyl alcohol; 4-Tolylcarbinol; ｱﾙｷﾙ(C = 1 ~ 3) ﾍﾞﾝｼﾞﾙｱﾙｺｰﾙ; *p*-メチルベンジルアルコール; (4-Methylphenyl)methanol; 4-(Hydroxymethyl)toluene; *p*-Tolualcohol; Methyl Benzyl Alcohol; *p*-Tolyl alcohol
4. **Molecular Formula:** $C_8H_{10}O$
5. **Molecular Weight:** 122.16
6. **RIFM Number:** 34

2. Physical data

1. **Boiling Point:** 217 °C (FMA database), 224.85 °C (US EPA, 2012a)
2. **Flash Point:** > 200 °F; CC (FMA database)
3. **Log K_{OW}:** 1.62 (US EPA, 2012a)
4. **Melting Point**: 60 °C (FMA database), 12.07 °C (US EPA, 2012a)
5. **Water Solubility:** 14260 mg/L (US EPA, 2012a)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00588 mm Hg @ 20 °C (US EPA, 2012a), 0.03 mm Hg @ 20 °C (FMA database), 0.0109 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 $L\,mol^{-1}\cdot cm^{-1}$)
9. **Appearance/Organoleptic:** White crystals, granular or crystalline powder, sometimes fused lumps; faint, but very pleasant green-rosy, leafy, and sweet-balsamic odor of moderate tenacity (Arctander Volume II, 1969)

3. Exposure

1. **Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0088% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0019 mg/kg/day or 0.12 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0019 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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, 2015, 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** 79.9%

Bronaugh et al., 1990: The skin absorption of read-across material [7–^{14}C] benzyl alcohol (CAS # 100-51-6; see Section 5) was measured in 4 female rhesus monkeys. The test material in acetone was applied at a concentration of 4 μg/cm^2 to a 1–cm^2 area of abdominal skin for 24 h. Urine was collected for an additional 4 days. The extent of dermal absorption was estimated from the amount of ^{14}C-equivalents excreted in the urine over the 5-day collection period. When the application site was occluded with either plastic wrap or a glass chamber, the absorption of benzyl alcohol was 56.3 ± 14.5% and 79.9 ± 7.4%, respectively. When the site was not occluded, the absorption was 31.6 ± 4.2%.

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
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Benzyl alcohol (CAS # 100-51-6)
   b. **Repeated Dose Toxicity:** Benzyl alcohol (CAS # 100-51-6)
   c. **Developmental and Reproductive Toxicity:** Benzyl alcohol (CAS # 100-51-6)
   d. **Skin Sensitization:** Benzyl alcohol (CAS # 100-51-6)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Benzyl alcohol (CAS # 100-51-6)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

There are no metabolism data on *p*-tolyl alcohol. Metabolism of the material was predicted using the rat liver S9 metabolism simulator (OECD QSAR Toolbox v3.3) (See Appendix). *p*-Tolyl alcohol was out of domain for both the *in vivo* rat and *in vitro* rat S9 simulators (OASIS TIMES v2.27.16). The prediction is not utilized when a material is out of the model's chemical space (the applicability domain). However, if expert judgment justifies the inclusion of the chemical, that will override the model's defined regions and the justification will be provided.

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

p-Tolyl alcohol is not reported to occur in food 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.

8. REACH dossier

Available; accessed 05/31/19.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for *p*-tolyl alcohol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.048
2	Products applied to the axillae	0.048
3	Products applied to the face/body using fingertips	0.048
4	Products related to fine fragrances	1.5
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.64
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.048
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.048
5D	Baby cream, oil, talc	0.016
6	Products with oral and lip exposure	0.048
7	Products applied to the hair with some hand contact	0.048
8	Products with significant ano-genital exposure (tampon)	0.016
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.53
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.53
10B	Aerosol air freshener	0.048
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.016
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For p-tolyl alcohol, the basis was the reference dose of 1.0 mg/kg/day, a skin absorption value of 79.9%, and a skin sensitization NESIL of 5900 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, *p*-tolyl alcohol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of *p*-tolyl alcohol was assessed in an Ames study conducted in compliance with GLP regulations by the National Toxicology Program (NTP) in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 were treated with *p*-tolyl alcohol at concentrations of 0, 100, 333, 1000, 1333, 3000, 6666, and 10000 μg/plate in the presence and absence of a metabolically-active S9 mixture. There were no significant increases observed in the number of revertant colonies in the strains tested at any concentration (Zeiger et al., 1992). Under the conditions of the study, *p*-tolyl alcohol was considered not mutagenic in the Ames test.

There are no studies assessing the clastogenicity of *p*-tolyl alcohol. Read-across material benzyl alcohol (CAS # 100-51-6; see Section 5) was assessed in an *in vivo* micronucleus assay conducted according to OECD TG 474. Groups of male ddY mice were administered benzyl alcohol in saline via a single intraperitoneal injection at doses of 0, 50, 100, and 200 mg/kg. In a subsequent experiment, the mice were given multiple injections every 24 h for 4 days at doses of 0 and 100 mg/kg. Animals were euthanized 24 h after the last administration, bone marrow was extracted, and smears prepared. No increase in the number of micronucleated polychromatic erythrocytes was observed (Hayashi et al., 1988). Under the conditions of the study, benzyl alcohol was considered to be non-clastogenic in the *in vivo* micronucleus test, and this can be extended to *p*-tolyl alcohol.

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

Additional References: National Toxicology Program, 1989; Florin et al., 1980; Ishidate et al., 1984; Ball et al., 1984; Kuroda et al., 1984a; Fluck et al., 1976; Mortelmans et al., 1986; Yoo (1986); Waters et al., 1982; Heck et al., 1989; Milvy and Garro, 1976; Rogan et al., 1986; McGregor et al., 1988; Kuroda et al., 1984b; Zeiger et al., 1990; Anderson et al., 1990; Myhr et al., 1990; Chakrabarti et al., 1993; Foureman et al., 1994; Yoshikawa (1996); Storer et al., 1996; Miyagawa et al., 1995; Sasaki et al., 2000; Uno et al., 1994; Kubo et al., 2002; Yasunaga et al., 2004; Oda et al., 1978; Elia et al., 1994; Miller et al., 2005; Demir et al., 2010; Hughes et al., 2012; Reus et al., 2012; Fowler et al., 2012.

Literature Search and Risk Assessment Completed On: 10/07/14.

10.1.2. Repeated dose toxicity

The MOE for *p*-tolyl alcohol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on *p*-tolyl alcohol. Read-across material benzyl alcohol (CAS # 100-51-6; see Section 5) has numerous repeated dose toxicity studies. Thirteen-week gavage subchronic toxicity studies were conducted with benzyl alcohol in rats and mice by the US NTP. The NOAEL was determined to be 100 mg/kg/day, based on a decrease in bodyweight gain (National Toxicology Program, 1989). **Therefore, the *p*-tolyl alcohol MOE is equal to the benzyl alcohol NOAEL in mg/kg/day divided by the total systemic exposure to *p*-tolyl alcohol, 100/0.0019 or 52631.**

In addition, the total systemic exposure for *p*-tolyl alcohol (1.9 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for a Cramer Class I material at the current level of use for the repeated dose toxicity endpoint.

Section 9 provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 1.0 mg/kg/day.

10.1.2.1.1. Derivation of reference dose (RfD). The RfD for *p*-tolyl alcohol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 100 mg/kg/day by the uncertainty factor, 100 = 1.0 mg/kg/day.

Additional References: RIFM, 2012a; Belsito et al., 2012; RIFM, 2012b; Cosmetic Ingredient Review, 2001; OECD SIDS, 2001: Benzoates; RIFM, 2001; National Toxicology Program, 1980; RIFM, 2009; Merriman et al., 2003; Hoshino (1940); Miller et al., 1983; Duncan and Jarvis, 1943; Foulon et al., 2005; deJouffrey et al., 2004; Jost (1953); MacMillan (1973); Duraiswami (1954); Nishihara et al., 2000; Blair et al., 2000; Teuchy et al., 1971; Bray et al., 1951; Bray et al., 1958;

McCloskey et al., 1986a; McCloskey (1987), McCloskey et al., 1986b; LeBel et al., 1988; Hotchkiss et al., 1992; Nasseri-Sina et al., 1992; Sloane (1965); Diack and Lewis, 1928; Snapper et al., 1925; Fisher (1985); McCormack et al., 1982; Jimbo (1983a); Jimbo et al., 1983b; Kasting et al., 1987; Procter and Gamble Company, 1996; Saiyasombati and Kasting, 2003; Miller et al., 2006; Boehnlein et al., 1994; Van Hulst et al., 1997; Mikulak et al., 1998; Gregoire et al., 2009; Menczel and Maibach, 1970; Menczel and Maibach, 1972; Barry et al., 1985; Meyer (1965); Anderson and Raykar, 1989; RIFM, 2012c; Meyer and Meyer, 1959; RIFM, 2012d.

Literature Search and Risk Assessment Completed On: 09/29/14.

10.1.3. Developmental and Reproductive Toxicity

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

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on *p*-tolyl alcohol. Read-across material benzyl alcohol (CAS # 100-51-6; see Section 5) has a gavage post-natal screening study conducted in mice which determined the developmental NOAEL to be 550 mg/kg/day, the only dosage tested (Hardin, 1986). In a separate gavage post-natal screening study conducted in mice at 750 mg/kg/day, reduced pup body weights were noted (Hardin et al., 1987). This effect occurred in the presence of significant maternal toxicity. **Therefore, the MOE for developmental toxicity is equal to the benzyl alcohol NOAEL in mg/kg/day divided by the total systemic exposure, 550/0.0019 or 289473.**

When correcting for skin absorption (see Section 4), the total systemic exposure to *p*-tolyl alcohol (1.9 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no reproductive toxicity data on *p*-tolyl alcohol. Read-across material benzyl alcohol (CAS # 100-51-6) has several gavage mouse post-natal screening studies; no maternal toxicity was observed at 550 mg/kg/day (Hardin, 1986), while significant maternal toxicity (mortality and adverse clinical signs) was observed when the dosage was increased to 750 mg/kg/day (Hardin et al., 1987). There are no male reproductive data on benzyl alcohol or on any other read-across material. When correcting for skin absorption (see Section 4), the total systemic exposure to *p*-tolyl alcohol (1.9 μg/kg/day) is below the TTC (30 μg/kg bw/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.

Table 1
Data Summary for benzyl alcohol as read-across for *p*-tolyl alcohol.

LLNA Weighted Mean EC3 Value μg/cm[b] [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm[b]	NOEL-HMT (induction) μg/cm[b]	LOEL[b] (induction) μg/cm[b]	WoE NESIL[c] μg/cm[b]
> 12500 [1]	weak	5906	6897	8858	5900

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

Additional References: RIFM, 2012a; Belsito et al., 2012; RIFM, 2012b; Cosmetic Ingredient Review, 2001; OECD SIDS, 2001: Benzoates; RIFM, 2001; National Toxicology Program, 1980; RIFM, 2009; Merriman et al., 2003; Hoshino (1940); Miller et al., 1983; Duncan and Jarvis, 1943; Foulon et al., 2005; deJouffrey et al., 2004; Jost (1953); MacMillan (1973); Duraiswami (1954); Nishihara et al., 2000; Blair et al., 2000; Teuchy et al., 1971; Bray et al., 1951; Bray et al., 1958; McCloskey et al., 1986a; McCloskey (1987), McCloskey et al., 1986b; LeBel et al., 1988; Hotchkiss et al., 1992; Nasseri-Sina et al., 1992; Sloane (1965); Diack and Lewis, 1928; Snapper et al., 1925; Fisher (1985); McCormack et al., 1982; Jimbo (1983a); Jimbo et al., 1983b; Kasting et al., 1987; Procter and Gamble Company, 1996; Saiyasombati and Kasting, 2003; Miller et al., 2006; Boehnlein et al., 1994; Van Hulst et al., 1997; Mikulak et al., 1998; Gregoire et al., 2009; Menczel and Maibach, 1970; Menczel and Maibach, 1972; Barry et al., 1985; Meyer (1965); Anderson and Raykar, 1989; RIFM, 2012c; Meyer and Meyer, 1959; RIFM, 2012d.

Literature Search and Risk Assessment Completed On: 09/29/14.

10.1.4. Skin sensitization

Based on the existing data and read-across material benzyl alcohol (CAS # 100-51-6), *p*-tolyl alcohol is considered a skin sensitizer with a defined NESIL of 5900 μg/cm^2.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for *p*-tolyl alcohol. Based on the existing data and read-across material benzyl alcohol (CAS # 100-51-6; see Section 5), *p*-tolyl alcohol is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In *in chemico* experimental studies with read-across material benzyl alcohol, little to no reactivity to cysteine-based peptides has been reported (Natsch et al., 2007 Natsch and Gfeller, 2008). Benzyl alcohol has been reported to be both positive and negative in guinea pig tests (Kashima et al., 1993a, b; Klecak et al., 1977; Klecak, 1979, 1985; Hausen et al., 1995; Hausen et al., 1992; Ishihara et al., 1986). Additionally, benzyl alcohol has been evaluated in the murine local lymph node assay (LLNA) and was reported to have an EC3 value > 50% (12500 μg/cm^2) (RIFM, 2005a). In a human maximization test (HMT), no skin sensitization reactions were observed with *p*-tolyl alcohol (RIFM, 1978). In a confirmatory human repeat insult patch test (HRIPT) with 5% *p*-tolyl alcohol, no reactions indicative of sensitization were observed in any of the 39 volunteers (RIFM, 1964). The dermal sensitization potential of read-across material benzyl alcohol has also been evaluated in the HRIPT and the HMT. The NOEL in the HRIPT was 5906 μg/cm^2, and the LOEL was 8858 μg/cm^2 in ethanol-contacting vehicles. In the HMAX, a NOEL of 6897 μg/cm^2 has been reported (RIFM, 2004a; RIFM, 1979; RIFM, 1970; RIFM, 2002; RIFM, 2003; RIFM, 2004b; RIFM, 2005b). Section 9 provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose 1.0 mg/kg/day (Table 1).

Additional References: Sharp, 1978.

Literature Search and Risk Assessment Completed On: 10/10/14.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, *p*-tolyl alcohol 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 alcohol in experimental models. UV/Vis absorption spectra indicate minor 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 alcohol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for *p*-tolyl alcohol were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, $1000\ L\ mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/09/17.

10.1.6. Local Respiratory Toxicity

There are no inhalation data available on *p*-tolyl alcohol. However, in 4-week repeat dose inhalation study for the read-across analog benzyl alcohol (CAS # 100-51-6; see section 5), a NOAEC of 1072 mg/m^3 was reported (RIFM, 2009).

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 4-week repeat dose inhalation study conducted in rats, a NOAEC of 1072 mg/m^3 was reported for benzyl alcohol (RIFM, 2009). There were no treatment-related macroscopic or microscopic findings at any concentration administered; therefore, the NOAEC was determined to be the highest concentration, 1072 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (1072 mg/m^3) × (1 m^3/1000 L) = 1.072 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (1.072 mg/L) × (61.2 L/day) = 65.61 mg/day
- (65.61 mg/day)/(0.0016 kg lung weight of rat*) = 41006.25 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.12 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford, 2015, 2017; Safford, 2015; Comiskey et al., 2017). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.18 mg/kg lung weight/day and resulting in an MOE of 227813 (i.e., [41006.25 mg/kg lung weight/day]/[0.18 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.12 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy", subsection, "Comparative Airway Anatomy."

Additional References: Carpenter et al., 1949; Smyth et al., 1951; DeGaulejac and Dervillee, 1938; Buchbauer et al., 1993; Buchbauer et al., 1992; Reynolds and Smith, 1995; Johnson et al., 2005; RIFM, 2001.

Literature Search and Risk Assessment Completed On: 07/01/16.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of *p*-tolyl alcohol 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 alcohol 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 alcohol as possibly being either persistent nor 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on current VoU (2015), *p*-tolyl alcohol does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. RIFM, 2017c**:** Ready biodegradability of the test material was evaluated in a 28-day DOC die-away study according to the OECD 301A method. Biodegradation of 98% was observed.

10.2.1.2.2. Ecotoxicity. RIFM, 2017a**:** An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50

was reported to be 89 mg/L based on yield. The 72-h NOEC was reported to be 10 mg/L for both growth rate and yield. The EC10 was reported to be 85 (77–96) mg/L and 35 (32–89) mg/L for growth and yield, respectively.

RIFM, 2017b**:** A *Daphnia magna* immobilization test (limit test) was conducted according to the OECD 202 EU C.2 method under static conditions. Based on the nominal concentrations, the 48-h EC50 was greater than 100 mg/L.

10.2.1.2.3. Other available data. *p*-Tolyl alcohol has been registered under REACH with no additional data at this time.

10.2.1.2.4. Risk assessment refinement. Since *p*-tolyl alcohol has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in µg/L).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (µg/L	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	352.9			1000000	0.3529	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.62	1.62
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 RQs for this material are < 1. No further assessment is necessary.

The RIFM PNEC is 0.3529 µg/L. The revised PEC/PNECs for EU and NA are not applicable and cleared at screening-level; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

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

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110842.

Appendix

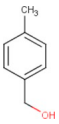
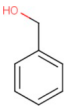
Read-across Justification

Methods

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

- The identified read-across analogs were confirmed by using expert judgment.

- The physical–chemical properties of the target material and read-across analogs were calculated using EPI Suite v4.11 developed by the US EPA (US EPA, 2012a).
- The J_{max} values were calculated using the RIFM skin absorption model (SAM), and the parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2018).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2018).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.1) (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2018).

	Target Material	Read-across Material
Principal Name	*p*-Tolyl alcohol	Benzyl alcohol
CAS No.	589-18-4	100-51-6
Structure		
Read-across Endpoint		• Genotoxicity • Repeated Dose • Developmental and reproductive • Skin sensitization • Respiratory
Molecular Formula	$C_8H_{10}O$	C_7H_8O
Molecular Weight	122.17	108.14
Melting Point (°C, EPI Suite)	12.07	−5.43
Boiling Point (°C, EPI Suite)	224.85	205.65
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.453	7.133
Log Kow (KOWWIN v1.68 in EPI Suite)	1.62	1.08
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.426e+004	4.105e+004
J_{max} (μg/cm^2/h, SAM)	175.570	643.343
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.024308	0.022028
Similarity (Tanimoto score)[1]		76%
Genotoxicity		
DNA Binding (OASIS v1.1)	• No alert found	• No alert found
DNA Binding (OECD)	• Michael addition • Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals • Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	• Michael addition • Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals • Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes
Carcinogenicity (genotox and non-genotox) Alerts (ISS)	• No alert found	• No alert found
DNA Alerts for Ames, MN, CA (OASIS v1.1)	• No alert found	• No alert found
***In Vitro* Mutagenicity (Ames test) alerts (-ISS)**	• No alert found	• No alert found
***In Vivo* Mutagenicity (Micronucleus) alerts (ISS)**	• No alert found	• No alert found
Oncologic Classification (OECD)	• Not classified	• Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	Not categorized	Not categorized
Developmental and Reproductive Toxicity		
ER Binding (OECD)	Non-binder, without OH or NH2 group	Non-binder, without OH or NH2 group
Developmental Toxicity Model (CAESAR v2.1.6)	Toxicant (moderate reliability)	Toxicant (low reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency (OECD)	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Model (CAESAR v2.1.6)	Sensitizer (moderate reliability)	Sensitizer (moderate reliability)
Local Respiratory Toxicity		
Respiratory Sensitization (OECD)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator *(OECD)*	See Supplemental Data 1	See Supplemental Data 2

[1] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).

Summary

There are insufficient toxicity data on *p*-tolyl alcohol (CAS # 589-18-4). Hence, *in silico* evaluation was conducted to determine the read-across material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, benzyl alcohol (CAS # 100-51-6) was identified as a read-across analog for the endpoints shown above.

Conclusions

- Benzyl alcohol (analog) was used as a read-across analog for *p*-tolyl alcohol (target material) based on the following:
- The target material and read-across analog belong to the generic class of aryl alcohols, and specifically, aryl alkyl alcohol.
- The target material and read-across analog contain the substructure of benzyl alcohol.
- The only difference is that the target material contains a methyl group in the *para* position. The differences between structures do not change the physical–chemical properties or raise any additional structural alerts. Therefore, the toxicity profiles are expected to be similar.
- The target material and read-across analog show similar alerts for DNA binding, mutagenicity, genotoxicity, and oncologic classification.
- The target material and read-across analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is a molecular initiating event analogous to protein binding.
- The target material and read-across analog show similar alerts for protein binding.
- The target material and read-across analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

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