Food and Chemical Toxicology 141 (2020) 111338

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, *p*-isopropylbenzyl alcohol, CAS Registry Number 536-60-7

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A B S T R A C T

Summary: **The existing information** supports **the use of this material as described in this safety assessment**. *p*-Isopropylbenzyl alcohol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the read-across analog benzyl alcohol (CAS # 100-51-6) show that *p*-isopropylbenzyl alcohol is not expected to be genotoxic. Data from the read-across analog benzyl alcohol (CAS # 100-51-6) provide a calculated MOE > 100 for the repeated dose, developmental, and local respiratory toxicity endpoints. 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). Data from read-across analog benzyl alcohol (CAS # 100-51-6) provided *p*-isopropylbenzyl alcohol a NESIL of 5900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity and photoallergenicity endpoints were evaluated based on UV spectra; *p*-isopropylbenzyl alcohol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *p*-isopropylbenzyl alcohol was found not to be a PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are < 1.

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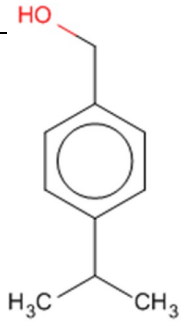
https://doi.org/10.1016/j.fct.2020.111338
Received 24 April 2019; Received in revised form 14 February 2020; Accepted 8 April 2020
Available online 24 April 2020

Version: 042419. This version replaces any previous versions.

Name: *p*-Isopropylbenzyl alcohol
CAS Registry Number: 536-60-7



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
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-Isopropylbenzyl alcohol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the read-across analog benzyl alcohol (CAS # 100-51-6) show that *p*-isopropylbenzyl alcohol is not expected to be genotoxic. Data from the read-across analog benzyl alcohol (CAS # 100-51-6) provide a calculated MOE > 100 for the repeated dose, developmental, and local respiratory toxicity endpoints. 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). Data from read-across analog benzyl alcohol (CAS # 100-51-6) provided *p*-isopropylbenzyl alcohol a NESIL of 5900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity and photoallergenicity endpoints were evaluated based on UV spectra; *p*-isopropylbenzyl alcohol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *p*-isopropylbenzyl alcohol was found not to be a 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 genotoxic. (Zeiger et al., 1990; Hayashi et al., 1988)
Repeated Dose Toxicity: NOAEL = 100 mg/kg/day. (NTP, 1989)
Developmental and Reproductive Toxicity: Developmental NOAEL = 550 mg/kg/day. No reproductive 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: 80% (OECD 301F)	RIFM, (2012a)
Bioaccumulation: Screening-level: 12.0 L/kg	(EPI Suite v.4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 135.7 mg/L	(RIFM Framework; Salvito et al., 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 et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 135.7 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.1357 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** *p*-Isopropylbenzyl alcohol
2. **CAS Registry Number:** 536-60-7
3. **Synonyms:** Benzenemethanol, 4-(1-methylethyl)-; Cumin alcohol; Cuminic alcohol; Cuminol; Cuminyl alcohol; p-Cymen-7-ol; p-iso-Propylbenzyl alcohol; ｱﾙｷﾙ(C = 1～3)ﾍﾞﾝｼﾞﾙｱﾙｺｰﾙ; (4-Isopropylphenyl)methanol; *p*-Isopropylbenzyl alcohol
4. **Molecular Formula:** $C_{10}H_{14}O$
5. **Molecular Weight:** 150.22
6. **RIFM Number:** 446

2. Physical data

1. **Boiling Point:** 248 °C (FMA database), 250.16 °C (US EPA, 2012a)
2. **Flash Point:** > 200 °F; CC (FMA database)
3. **Log K_{OW}:** Log Pow = 2.2 (RIFM, 2013), 2.53 (US EPA, 2012a)
4. **Melting Point**: 23.23 °C (US EPA, 2012a)
5. **Water Solubility:** 1687 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.9782 (RIFM Database), 0.976 (FMA database)
7. **Vapor Pressure:** 0.00167 mm Hg @ 20 °C (US EPA, 2012a), 0.02 mm Hg 20 °C (FMA database), 0.00316 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No absorbance in the region 290–400 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid with a spicy odor (Arctander, 1969)

3. Exposure

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Co**ncentration in Hydroalcoholics**:** 0.0071% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000014 mg/kg/day or 0.0010 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00014 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 et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 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 V) 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*-isopropylbenzyl alcohol. Metabolism of the material was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.3) (See Appendix). *p*-Isopropylbenzyl 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 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-Isopropylbenzyl alcohol is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):

Angelica (*Angelica archangelica* L.) Black currants (*Ribes nigrum* L.) Calabash nutmeg (*Monodora myristica* Dunal) Cardamom (*Ellettaria cardamomum* Maton.) Cherimoya (Annona cherimolia Mill.) Citrus

fruits Cumin seed (Cuminum cyminum L.) Curcuma species Dill (Anethum species) Eucalyptus oil (Eucalyptus globulus Labill) Grape brandy Honey Laurel (*Laurus nobilis* L.) Licorice (*Glycyrrhiza glabra* L.) Lovage (*Levisticum officinale* Koch) Mastic (*Pistacia lentiscus*) Mentha oils Nutmeg (*Myristica fragrans* Houttuyn) Origanum (Spanish) (Coridothymus cap. (L.) Rchb.) Raspberry, blackberry, and boysenberry Thyme (Thymus species) Tomato (Lycopersicon esculentum Mill.) Turpentine oil (Pistacia terebinthus) Vaccinium species Wine.

*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

Pre-registered for 11/30/10; no dossier available as of 04/24/19.

9. Conclusion

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

IFRA Category[b]	Descript[a]on of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.45
2	Products applied to the axillae	0.14
3	Products applied to the face/body using fingertips	0.40
4	Products related to fine fragrances	2.5
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	0.64
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.64
5D	Baby cream, oil, talc	0.21
6	Products with oral and lip exposure	1.5
7	Products applied to the hair with some hand contact	0.80
8	Products with significant ano-genital exposure (tampon)	0.21
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.0
10A	Household care products with mostly hand contact (hand dishwashing detergent)	2.0
10B	Aerosol air freshener	4.8
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.21
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

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*-isopropylbenzyl 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. Human health endpoint summaries

10.1. Genotoxicity

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

10.1.1. Risk assessment

There are no studies assessing the mutagenicity of *p*-isopropylbenzyl alcohol.

The mutagenic activity of read-across material benzyl alcohol (CAS # 100-51-6; see Section V) was assessed in an Ames study conducted in compliance with GLP regulations by the NTP in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were treated with benzyl alcohol at concentrations of 0, 100, 333, 1000, 1333, 3000, and 6666 μg/plate in the presence and absence of metabolically active microsomal mix (S9 mix). There were no significant increases observed in the number of revertant colonies in the strains tested at any concentration (Zeiger et al., 1990). Under the conditions of the study, benzyl alcohol was considered not mutagenic in the Ames test. This was confirmed in an *in vitro* mammalian gene mutation test using mouse lymphoma L5178Y cells. Benzyl alcohol up to concentrations of 5000 μg/mL was unable to induce a dose-related, statistically significant increase in mutation frequency and was considered not mutagenic in the *in vitro* mammalian gene mutation test.

There are no studies assessing the clastogenic activity of *p*-isopropylbenzyl alcohol. The clastogenic activity of read-across material benzyl alcohol (CAS # 100-51-6; see Section V) was assessed in an *in vivo* micronucleus assay conducted equivalent to OECD TG 474. Groups of male ddY mice were administered benzyl alcohol in saline via either a single intraperitoneal injection at the concentrations of 0, 50, 100, and 200 mg/kg body weight or multiple injections every 24 h for 4 days at concentrations of 0 and 100 mg/kg body weight. Animals were euthanized 24 h after last administration, bone marrow was extracted, and smears were 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 unable to induce micronuclei in the *in vivo* micronucleus test.

Based on the available data, benzyl alcohol does not present a concern for genotoxic potential, and this can be extended to *p*-isopropylbenzyl alcohol.

Additional References: Rockwell and Raw, 1979; NTP, 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; Rockwell and Raw, 1979.

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

10.2. Repeated dose toxicity

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

10.2.1. Risk assessment

There are no repeated dose toxicity data on *p*-isopropylbenzyl

alcohol. Read-across material benzyl alcohol (CAS # 100-51-6; see Section V) has numerous repeated dose toxicity studies. Gavage 13-week subchronic toxicity studies were conducted with benzyl alcohol in rats and mice by the US National Toxicology Program (NTP). The NOAEL was determined to be 100 mg/kg/day, based on reduced bodyweight gain (NTP, 1989; data also available in National Toxicology Program, 1980a). **Therefore, the MOE is equal to the benzyl alcohol NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.00014 or 714286.**

In addition, the total systemic exposure for *p*-isopropylbenzyl alcohol (0.14 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) at the current level of use for the repeated dose toxicity endpoint.

Section IX 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.

The RfD for *p*-isopropylbenzyl alcohol was calculated by dividing the NOAEL of 100 mg/kg/day by the uncertainty factor, 100 = 1.0 mg/kg/day.

Additional References: RIFM, 2012d; Belsito et al., 2012; Meyer and Meyer, 1959; Meyer (1965); RIFM, 2012c; CIR, 2001; OECD SIDS, 2001: Benzoates; RIFM et al., 2001; NTP, 1980b; 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; RIFM, 2009; Menczel, 1970; Menczel and Maibach, 1972; Barry et al., 1985; Anderson and Raykar, 1989; RIFM, 2012b; Gaunt et al., 1982; Gaunt et al., 1979; RIFM, 2012e; Laws et al., 2006; Robinson et al., 1954; Gruneberg and Langecker, 1957; Chakraborty and Smith, 1967.

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

10.3. Developmental and reproductive toxicity

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

There are insufficient reproductive toxicity data on *p*-isopropylbenzyl alcohol or any read-across materials. The exposure is below the TTC for a Cramer class I material.

10.3.1. Risk assessment

There are no developmental toxicity data on *p*-isopropylbenzyl alcohol. Read-across material benzyl alcohol (CAS # 100-51-6; see Section V) has a gavage postnatal screening study conducted in mice that determined the developmental NOAEL to be 550 mg/kg/day, the only dosage tested (Hardin, 1986). In a separate gavage postnatal screening study conducted in mice at 750 mg/kg/day, reduced pup body weights were noted (Hardin et al., 1987; data also available in National Institute for Occupational Safety and Health, 1983). 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, 550/0.00014 or 3928571.**

In addition, the total systemic exposure for *p*-isopropylbenzyl alcohol (0.14 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) at the current level of use for the developmental toxicity endpoint.

There are no reproductive toxicity data on *p*-isopropylbenzyl alcohol. Read-across material benzyl alcohol (CAS # 100-51-6) has several gavage mouse postnatal 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; data also available in National Institute for Occupational Safety and Health, 1983). There are no male reproductive data on benzyl alcohol or any other read-across material. When correcting for skin absorption (see Section IV), the total systemic exposure (0.14 μg/kg/day) is below the TTC for *p*-isopropylbenzyl alcohol (30 μg/kg bw/day).

Additional References: RIFM, 2012d; Belsito et al., 2012; Meyer and Meyer, 1959; Meyer (1965); RIFM, 2012c; CIR, 2001; OECD SIDS, 2001: Benzoates; RIFM et al., 2001; NTP, 1980b; 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; RIFM, 2009; Menczel, 1970; Menczel and Maibach, 1972; Barry et al., 1985; Anderson and Raykar, 1989; RIFM, 2012b; Gaunt et al., 1982; Gaunt et al., 1979; RIFM, 2012e; Laws et al., 2006; Robinson et al., 1954; Gruneberg and Langecker, 1957; Chakraborty and Smith, 1967.

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

10.4. Skin sensitization

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

10.4.1. Risk assessment

In *in chemico* experimental studies, little to no reactivity to cysteine-based peptides has been reported with read-across material benzyl alcohol (CAS # 100-51-6; see Section V) (Natsch et al., 2007; Natsch and Gfeller, 2008). Read-across material benzyl alcohol has been reported to be both positive and negative in guinea pig tests. Additionally, in a local lymph node assay, read-across material benzyl alcohol was reported to have an EC3 value > 50% (12500 μg/cm^2) (RIFM, 2005a). In the human repeat insult patch test, read-across material benzyl alcohol had a NESIL of 5906 μg/cm^2 and a LOEL of 8858 μg/cm^2 in ethanol contacting vehicles (RIFM, 2005b; RIFM, 2004). In the HMAX, a NOEL of 6897 μg/cm^2 has been reported with read-across material benzyl alcohol (Epstein 1979; #1697; RIFM, 1970) and 2759 μg/cm^2 with *p*-isopropylbenzyl alcohol (RIFM, 1973).

Based on the material-specific data and read-across to benzyl alcohol (CAS # 100-51-6; see Section V), *p*-isopropylbenzyl alcohol is considered to be a weak skin sensitizer with a defined NESIL of 5900 μg/cm^2 (Table 1). Section IX 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

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

LLNA weighted mean EC3 value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
> 12500 [1]	weak	5906	6897	8858	5900

NOEL = No observed effect level; HRIP = Human Repeat Insult Patch Tes; 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.

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.

Additional References: None.

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

10.5. Phototoxicity/photoallergenicity

Based on the available UV spectra, *p*-isopropylbenzyl alcohol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.5.1. Risk assessment

There are no phototoxicity studies available for *p*-isopropylbenzyl alcohol in experimental models. UV absorption spectra indicate no absorbance between 290 and 400 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*-isopropylbenzyl alcohol does not present a concern for phototoxicity or photoallergenicity.

10.5.2. UV spectra analysis

The available spectra indicate no absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

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

10.6. Local respiratory toxicity

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

10.6.1. 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 test substance-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) × (1m^3/1000L) = 1.072 mg/L
- Minute ventilation (MV) 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 0.0010 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; 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 0.0015 mg/kg lung weight/day resulting in an MOE of 27337500 (i.e., [41006.25 mg/kg lung weight/day]/[0.0015 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.0010 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 et al., 2001.

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

10.7. Environmental endpoint summary

10.7.1. Screening-level assessment

A screening-level risk assessment of *p*-isopropylbenzyl alcohol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (US EPA, 2012b; providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, *p*-isopropylbenzyl 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*-isopropylbenzyl alcohol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria

Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

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

10.7.1.2. Key studies

10.7.1.2.1. Biodegradation. **RIFM, 2012a:** The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F method. Under the conditions of the study, biodegradation of 80% was observed after 28 days.

10.7.1.2.2. Ecotoxicity. **RIFM, 2000:** A *Daphnia magna* acute toxicity test was conducted according to the OECD 202I method under static conditions. The 48-h EC50 was reported to be 1.3 mg/L.

10.7.1.2.3. Other available data. *p*-Isopropylbenzyl alcohol has been pre-registered for REACH with no additional data at this time.

10.7.2. Risk assessment refinement

Since *p*-isopropylbenzyl alcohol passed the screening criteria, measured data is included in this document for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>135.7</u>			1,000,000	0.1357	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.2	2.2
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.1357 μg/L. The revised PEC/PNECs for EU and NA not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/05/19.

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 01/22/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111338.

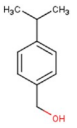
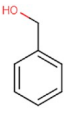
Appendix

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).

- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target and analogs were calculated using EPI Suite v4.11 developed by US EPA (US EPA, 2012a).
- The J_{max} values were calculated using the RIFM skin absorption model (SAM). 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, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012).
- 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, 2012).
- The major metabolites for the target material and read across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012).

	Target Material	Read-across Material
Principal Name	*p*-Isopropylbenzyl alcohol	Benzyl alcohol
CAS No.	536-60-7	100-51-6
Structure		
Read-across endpoint		• Genotoxicity • Repeated dose toxicity • Developmental toxicity • Skin sensitization • Local respiratory toxicity
Molecular Formula	$C_{10}H_{14}O$	C_7H_8O
Molecular Weight	150.22	108.14
Melting Point (°C, EPI Suite)	23.23	−5.43
Boiling Point (°C, EPI Suite)	250.16	205.65
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.4213	7.133
Log Kow (KOWWIN v1.68 in EPI Suite)	2.53	1.08
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1687	4.105e+004
J_{max} (μg/cm^2/h, SAM)	151.5096777	978.9489605
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.04284	0.022028
Similarity (Tanimoto score)		66%
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)
Metabolism		
Rat liver S9 Metabolism Simulator (OECD)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on *p*-isopropylbenzyl alcohol (CAS # 536-60-7). Hence, *in silico* evaluation was conducted to determine a read-across material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, the above shown read-across material was identified as analogs with sufficient data for toxicological evaluation.

Conclusions

- Benzyl alcohol (analog) was used as a read-across analog for *p*-isopropylbenzyl alcohol (target) based on:
  - o The target and analog belong to the generic class of aryl alcohol, specifically, aryl alkyl alcohol.
  - o The target and analog contain the substructure of benzyl alcohol.
  - o The only difference is that the target contains an isopropyl group in the para position. The differences between structures do not essentially change the physical–chemical properties nor raise any additional structural alerts, and therefore, the toxicity profiles are expected to be similar.
  - o The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity, and oncologic classification.
  - o The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER binding. ER binding is a molecular initiating event.
  - o The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

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