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Short review

RIFM fragrance ingredient safety assessment, Benzyl alcohol, CAS Registry Number 100-51-6

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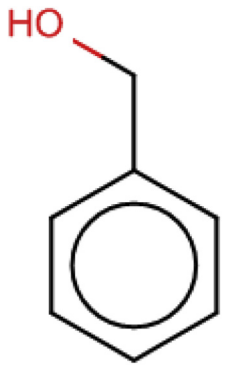


Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th **percentile** – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF – Assessment Factor
BCF – Bioconcentration factor
DEREK – Derek nexus is an *in silico* tool used to identify structural alerts
DST – Dermal Sensitization Threshold
EC3 Value – The estimated concentration required to produce a 3 fold increase in draining lymph-node cell proliferative activity.
ECHA – European Chemicals Agency
EU – Europe/European Union
GLP – Good Laboratory Practice
IFRA – The International Fragrance Association
LOEL – Lowest Observable Effect Level
MOE – Margin of Exposure
MPPD – Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL – No Expected Sensitization Induction Level
NOAEC – No Observed Adverse Effect Concentration
NOAEL – No Observed Adverse Effect Level
NOEC – No Observed Effect Concentration
OECD – Organisation for Economic Co-operation and Development
OECD TG – Organisation for Economic Co-operation and Development Testing Guidelines
PBT – Persistent, Bioaccumulative, and Toxic
PEC/PNEC – Predicted Environmental Concentration/Predicted No Effect Concentration
QRA – quantitative risk assessment
REACH – Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM – Research Institute for Fragrance Materials
RQ – Risk Quotient
TTC – Threshold of Toxicological Concern
UV/Vis Spectra – Ultra Violet/Visible spectra
VCF – Volatile Compounds in Food
VoU – Volume of Use
vPvB – (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on RIFM's Criteria Document (Api et al., 2015) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 100 mg/kg/day. Gavage 13-week subchronic toxicity studies conducted in rats and mice resulted in a MOE of 2778 while considering 79.9% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

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: NOAEL = 500 mg/kg/day (Kieckebusch and Lang, 1960)
Skin Sensitization: NESIL = 5900 μg/cm^2 (RIFM, 2005b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 1072 mg/m^3 (1.07 mg/L) (RIFM, 2009)
Environmental Safety Assessment
Hazard Assessment:

(*continued*)

Persistence: Critical Measured Value: 95.8% (OECD 301B)	(RIFM, 1993)
Bioaccumulation: Screening level: 1.371 L/k	(EpiSuite ver 4.1)
Ecotoxicity: Screening level: 96 h Algae EC50: 48.31 mg/l	(EpiSuite ver 4.1)
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: 96 h Algae EC50: 48.31 mg/l	(EpiSuite ver 4.1)
RIFM PNEC is: 4.831 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe <1	

1. Identification

1. **Chemical Name:** Benzyl alcohol
2. **CAS Registry Number:** 100-51-6
3. **Synonyms:** Benzenemethanol, Benzyl alcohol, α-Hydroxytoluene, Phenyl carbinol, Phenylmethyl alcohol, Phenylmethanol, Phenylcarbinol, α-Toluenol, Benzylic alcohol, ﾍﾞﾝｼﾞﾙｱﾙｺｰﾙ
4. **Molecular Formula:** C_7H_8O
5. **Molecular Weight:** 108.14
6. **RIFM Number:** 107

2. Physical data

1. **Boiling Point:** 205 °C [FMA database], 205.65 °C [EPI Suite]
2. **Flash Point:** >212 °F; CC [FMA database]
3. **Log K_{OW}:** 1.10 (Abraham and Rafols, 1995), 1.10 [Patel et al., 2002], 1.1 [RIFM, 1996], 1.08 [EPI Suite]
4. **Melting Point**: −5.43 °C [EPI Suite]
5. **Water Solubility:** 41050 mg/L [EPI Suite]
6. **Specific Gravity:** 1.042–1.047 [FMA database], 1.044–1.049 [FMA database], 1.05 g/ml [RIFM, 1994]
7. **Vapor Pressure:** 0.0331 mm Hg @ 20 °C [EPI Suite 4.0], 0.07 mm Hg 20 °C [FMA database], 0.0535 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Minor absorption in the region of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1}).
9. **Appearance/Organoleptic:** A clear, colorless to very pale yellow liquid having a slight aromatic odor.

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year	(IFRA, 2011)
2. **Average Maximum Concentration in Hydroalcoholics:** 3.89%	(IFRA, 2004)
3. **97.5**th **Percentile:** 1.65%	(IFRA, 2004)
4. **Dermal Exposure*:** 0.042 mg/kg/day	(IFRA, 2004)
5. **Oral Exposure:** Not available	
6. **Inhalation Exposures**:** 0.0026 mg/kg/day	(IFRA, 2004)
7. **Total Systemic Exposure (Dermal + Inhalation):** (0.042 mg/kg/day × 79.9% absorption) + 0.0026 mg/kg/day = 0.036 mg/kg/day	

*Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

**Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1. **Dermal:** 79.9%

Bronaugh et al. (1990): The skin absorption of [7–^{14}C] benzyl alcohol 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:** Data not available – not considered.
3. **Inhalation:** Assumed 100%
4. **Total:** Dermal (79.9%) + Inhalation (assume 100%) absorbed = (0.042 mg/kg/day × 79.9%) + 0.0026 mg/kg/day = 0.036 mg/kg/day

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. **Analogues Selected:**
a. Genotoxicity: None
b. Repeated Dose Toxicity: None
c. **Developmental and Reproductive Toxicity:** Benzyl acetate (CAS # 140-11-4); benzoic acid (CAS # 65-85-0)
d. Skin Sensitization: None
e. Phototoxicity/Photoallergenicity: None
f. Local Respiratory Toxicity: None
g. Environmental Toxicity: None
3. **Read across justifications:** See Appendix below

6. Metabolism

Chidgey et al. (1986): The metabolism of benzyl acetate was investigated in male Fischer 344 rats. Rats were dosed by gavage with [methylene-(14)C] benzyl acetate (500 mg/kg) alone or together with metabolic inhibitors. Benzyl acetate is rapidly hydrolyzed to benzyl alcohol, which is oxidized to benzaldehyde, and then further oxidized to benzoic acid. Benzoic acid is conjugated with glycine to yield the major urinary excretion product of hippuric acid, or it is conjugated with glucuronic acid to yield benzoyl glucuronide.

Yuan et al. (1995): Effects of gavage versus dosed feed administration on the toxicokinetics of benzyl acetate were studied in male rats and mice. Benzyl acetate was rapidly hydrolyzed to benzyl alcohol and then oxidized to benzoic acid.

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

Benzyl alcohol is reported to occur in the following foods* and some natural complex substances (NCS):

Cinnamomum species	Mustard, brown (Brassica spp.)
Cinnamon bark (Cinnamomum zeylanicum Blume)	Mustard, yellow (Brassica spp.)
Dent corn oil	Red sage (Texas sage) (S. coccinea Juss. ex Murr.)
Maize (Zea mays L.)	Salvia species

*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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

IFRA Standard Restricted – The use of this material should be limited quantitatively. See Skin Sensitization.

9. REACH dossier

Available: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d9b1369-7454-687c-e044-00144f67d249/DISS-9d9b1369-7454-687c-e044-00144f67d249_DISS-9d9b1369-7454-687c-e044-00144f67d249.html, accessed on 07/20/2015.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, Benzyl alcohol does not present a concern for genetic toxicity.

10.1.2. Risk assessment

The mutagenic activity of benzyl alcohol 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 TA 98, TA 100, TA 1535 and TA 1537 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 (S-9 mix). There were no significant increases observed in the number of revertant colonies in the strains 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.

The clastogenic activity of benzyl alcohol 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 four 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 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.

Additional References: Milvy and Garro, 1976; Rogan et al., 1986; Heck et al., 1989; Mortelmans et al., 1986; Florin et al., 1980; Ball et al., 1984; Ishidate et al., 1984; Kuroda et al., 1984; Miller et al., 2005; Kubo et al., 2002; Uno et al., 1994; Elia et al., 1994; Oda et al., 1978; Yasunaga et al., 2004; Sasaki et al., 2000; Hughes et al., 2012; Reus et al., 2012; Fowler et al., 2012; NTP, 1989; Demir et al., 2010; Yoo, 1985, 1986; Fluck et al., 1976; Waters et al., 1982; McGregor et al., 1988; Anderson et al., 1990; Chakrabarti et al., 1993; Demir et al., 2010.

Literature Search and Risk Assessment Completed on: 06/03/14.

10.1.3. Repeated dose toxicity

The margin of exposure for Benzyl alcohol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

There are numerous repeated dose toxicity studies with benzyl alcohol. Gavage 13-week 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 reduced body weight gain (NTP, 1989; data also available in NTP, 1980). Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.036 or 2778.

Additional References: Scognamiglio et al., 2012a; Belsito et al., 2012a; CIR, 2001; OECD SIDS, 2001: Benzoates; RIFM, 2001; NTP, 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, 1958; McCloskey et al., 1986a, 1986b; RIFM, 1987b; LeBel et al., 1988; Hotchkiss et al., 1992b; Nasseri-Sina et al., 1992; Sloane, 1965; Diack and Lewis, 1928; Snapper et al., 1925; Fisher, 1985; McCormack et al., 1982; Jimbo, 1983; Jimbo et al., 1983; Kasting et al., 1987; RIFM, 1996; Saiyasombati and Kasting, 2003; Miller et al., 2006; Boehnlein et al., 1994; Van Hulst et al., 1997; Mikulak et al., 1998; Gregoire, 2009; Menczel and Maibach, 1970, 1972; Barry et al., 1985; Meyer, 1965; Anderson and Raykar, 1989; Scognamiglio et al., 2012b; Owston et al., 1981; RIFM, 1979b; RIFM, 2010; Politano et al., 2011, 2013a; RIFM, 1986b; RIFM, 1987a; RIFM, 1988a; RIFM, 1988b; RIFM, 1990a; Ford et al., 1987a; Ford, 1990a; Scognamiglio et al., 2012c; CIR, 1990; CIR, 2008; RIFM, 2000; RIFM, 1985b; Zaitsev and Rakhmanina, 1974; Johannsen and Purchase, 1969; RIFM, 2013a; Rumyantsev et al., 1987; Moro et al., 1969; Mankes et al., 1983, 1984, 1985; Maganova and Saitsev, 1973; Politano et al., 2013b; RIFM, 1985a; RIFM, 1986d; RIFM, 1988c; Ford et al., 1987b, 1990a, 1990b; Burdock et al., 1987; Chakraborty and Smith, 1967; Matsui, 1997; Landsiedel et al., 2002; Ikemoto et al., 2002; Brossmer et al., 1973; Thierfelder and Schempp, 1917; Bray et al., 1958; El Masry et al., 1956; Diez-Salez et al., 1993; Hotchkiss et al., 1992b, 1998; Lopez et al., 1998; Meyer, 1965; Schmitt et al., 2009; Ishiguro et al., 1993; EPA Hazard Characterization Document: Benzyl derivatives; McGinty et al., 2012; Belsito et al., 2012b; RIFM, 2013b; RIFM, 1986c; RIFM, 1957; Abdo and Wenk, 1995; Abdo et al., 1998; Longnecker et al., 1986; Longnecker et al., 1990; Young, 1989; Abdo et al., 1985; Caldwell et al., 1987; Chidgey et al., 1986; Grundschober, 1977; Miyashita and Robinson, 1980; Chidgey et al., 1987; McMahon et al., 1989a; Augustinsson and Ekedahl, 1962; Clapp and Young, 1970; McMahon et al., 1989b; Schunk et al., 1986; RIFM, 1989a; Hotchkiss et al., 1992c, 1992d; Caldwell et al., 1987; Meyer, 1965; Garnett et al., 1994; Hotchkiss et al., 1988, 1990a, 1990b, 1989; Hotchkiss et al., 1990a; Hotchkiss et al., 1990b; RIFM, 1989b; Hotchkiss, 1992a; FFHPVC: Benzyl Derivatives; OECD SIDS, 1994: Benzaldehyde; Kluwe et al., 1983; RIFM, 1990b; Peresedov, 1974; Hagan et al., 1967; Bar and Griepentrog, 1967; Sporn et al., 1967; Laham et al., 1991; Hruban et al., 1966; Schafer and Bowles, 1985; Taylor et al., 1964; Hoshino, 1940; Schweinsberg et al., 1986; MacEwen, 1986; Abramovici and Rachmuth-Roizman, 1983; Nishihara et al., 2000; SCCNFP, 2002; WHO, 2000; Kreis et al., 1971; Bedford and Clarke, 1972; Hruban et al., 1966; Graham and Kuizenga, 1945; Shtenberg and Ignat'ev, 1970; ECHA REACH Dossier: Benzoic acid; Sodemoto and Enomoto, 1980; Lemini et al., 1995; Kimmel et al., 1971; Ashby et al., 1997; Bedford and Clarke, 1971; Benton et al., 1955; Schafer and Bowles, 1985; Dawson et al., 1996; Nishihara et al., 2000; Picard et al., 2001; Kolle et al., 2010; Minor and Becker, 1971; Verrett et al., 1980; Daston et al., 1995; Peterka et al., 1986; Okubo and Kano, 2003; CIR, 2006; WHO, 1996; Lacroix et al., 2002; Kutzman et al., 1980, 1978; Bray et al., 1951; Laham et al., 1988; Laham and Potvin, 1987; Smith and Packer, 1972; Walkenstein and Weinhouse, 1953; Sherwin and Crowdle, 1922; Chidgey and Caldwell, 1986.

Literature Search and Risk Assessment Completed on: 05/30/14.

10.1.5. Developmental and reproductive toxicity

The margin of exposure for Benzyl alcohol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.6. Risk assessment

The developmental toxicity data on benzyl alcohol are sufficient for the developmental toxicity endpoint. A gavage post-natal screening study conducted in mice determined the developmental NOAEL to be 550 mg/kg/day, the only dosage tested (RIFM, 1986a). 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; data also available in RIFM, 1983). This effect occurred in the presence of significant maternal toxicity. Therefore, the MOE for developmental toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 550/0.036 or 15278.

The reproductive toxicity data on benzyl alcohol are insufficient for the reproductive toxicity endpoint. In gavage mouse post-natal screening studies, no maternal toxicity was observed at 550 mg/kg/day (RIFM, 1986a), 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 RIFM, 1983). There are no male reproductive toxicity data on benzyl alcohol. Benzyl acetate (CAS # 140-11-4; see Section V) is rapidly hydrolyzed to benzyl alcohol, which is

Table 2
Acceptable exposure limits – benzyl alcohol.

IFRA Category[a]	Examples of product type	Calculated QRA
1	Lip Products	0.2%
2	Deodorant/Antiperspirant	0.2%
3	Hydroalc., Shaved Skin	0.9%
4	Hydroalc., Unshaved Skin	2.7%
5	Women Facial Cream	1.4%
6	Mouthwash	4.3%
7	Intimate Wipes	0.4%
8	Hair Styling Aids Non-Spray	2.0%
9	Conditioners, Rinse-off	5.0%
10	Hard Surface Cleaners	2.5%
11	Candle (Non-Skin/Incidental Skin)	Not Restricted

[a] For a description of the categories, refer to the QRA Informational Booklet. (www.rifm.org/doc/QRAInfoJuly201.pdf).

Table 1
Data Summary for benzyl 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
>12,500 [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 three significant figures.

then oxidized to benzoic acid (CAS # 65-85-0; see Section V) (numerous references, metabolic scheme detailed in Chidgey et al., 1986; Yuan et al., 1995; see Section 6). Precursor benzyl acetate has 13-week dietary subchronic toxicity studies in rats and mice in which sperm morphology and vaginal cytology examinations were evaluated (Morrissey et al., 1988; data also available in NTP, 1993). There were no effects on sperm parameters in mice or rats up to the high dosage of 7900 or 3900 mg/kg/day, respectively. There were no effects on estrous cycling in female rats up to the high dosage of 4500 mg/kg/day. Lengthening of the estrous cycle occurred in high-dose female mice (9400 mg/kg/day), which the authors concluded was related to decreases in body weight. For the benzoic acid metabolite, a dietary chronic toxicity and 4-generation reproductive toxicity study conducted in rats determined the NOAEL for reproductive toxicity to be 1%, or 500 mg/kg/day, the highest dosage tested (Kieckebusch and Lang, 1960). These data indicate no specific concern for reproductive toxicity. The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE for reproductive toxicity is equal to the benzoic acid NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.036 or 13889.

Additional References: Scognamiglio et al., 2012a; Belsito et al., 2012a; CIR, 2001; OECD SIDS, 2001: Benzoates; RIFM, 2001; NTP, 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, 1958; McCloskey et al., 1986a, 1986b; RIFM, 1987b; LeBel et al., 1988; Hotchkiss et al., 1992b; Nasseri-Sina et al., 1992; Sloane, 1965; Diack and Lewis, 1928; Snapper et al., 1925; Fisher, 1985; McCormack et al., 1982; Jimbo, 1983; Jimbo et al., 1983; Kasting et al., 1987; RIFM, 1996; Saiyasombati and Kasting, 2003; Miller et al., 2006; Boehnlein et al., 1994; Van Hulst et al., 1997; Mikulak et al., 1998; Gregoire, 2009; Menczel and Maibach, 1970, 1972; Barry et al., 1985; Meyer, 1965; Anderson and Raykar, 1989; Scognamiglio et al., 2012b; Owston et al., 1981; RIFM, 1979b; RIFM, 2010; Politano et al., 2011, 2013a; RIFM, 1986b; RIFM, 1987a; RIFM, 1988a; RIFM, 1988b; RIFM, 1990a; Ford et al., 1987a; Ford, 1990a; Scognamiglio et al., 2012c; CIR, 1990; CIR, 2008; RIFM, 2000; RIFM, 1985b; Zaitsev and Rakhmanina, 1974; #3530; Johannsen and Purchase, 1969; RIFM, 2013a; Rumyantsev et al., 1987; Moro et al., 1969; Mankes et al., 1983, 1984, 1985; Maganova and Saitsev, 1973; Politano et al., 2013b; RIFM, 1985a; RIFM, 1986d; RIFM, 1988c; Ford et al., 1987b, 1990a, 1990b; Burdock et al., 1987; Chakraborty and Smith, 1967; Matsui, 1997; Landsiedel et al., 2002; Ikemoto et al., 2002; Brossmer et al., 1973; Thierfelder and Schempp, 1917; Bray et al., 1958; El Masry et al., 1956; Diez-Salez et al., 1993; Hotchkiss et al., 1992b, 1998; Lopez et al., 1998; Meyer, 1965; Schmitt et al., 2009; Ishiguro et al., 1993; EPA Hazard Characterization Document: Benzyl derivatives; McGinty et al., 2012; Belsito et al., 2012b; RIFM, 2013b; RIFM, 1986c; RIFM, 1957; Abdo and Wenk, 1995; Abdo et al., 1998; Longnecker et al., 1986; Longnecker et al., 1990; Young, 1989; Abdo et al., 1985; Caldwell et al., 1987; Chidgey et al., 1986; Grundschober, 1977; Miyashita and Robinson, 1980; Chidgey et al., 1987; McMahon et al., 1989a; Augustinsson and Ekedahl, 1962; Clapp and Young, 1970; McMahon et al., 1989b; Schunk et al., 1986; RIFM, 1989a; Hotchkiss et al., 1992c, 1992d; Caldwell et al., 1987; Meyer, 1965; Garnett et al., 1994; Hotchkiss et al., 1988, 1990a, 1990b, 1989; Hotchkiss et al., 1990a; Hotchkiss et al., 1990b; RIFM, 1989b; Hotchkiss et al., 1992a; FFHPVC: Benzyl Derivatives; OECD SIDS, 1994: Benzaldehyde; Kluwe et al., 1983; RIFM, 1990b; Peresedov, 1974; Hagan et al., 1967; Bar and Griepentrog, 1967; Sporn et al., 1967; Laham et al., 1991; Hruban et al., 1966; Schafer and Bowles, 1985; Taylor et al., 1964; Hoshino, 1940; Schweinsberg et al., 1986; MacEwen, 1986; Abramovici and Rachmuth-Roizman, 1983; Nishihara et al., 2000; SCCNFP, 2002; WHO, 2000; Kreis et al., 1971; Bedford and Clarke, 1972; Hruban et al., 1966; Graham and Kuizenga, 1945; Shtenberg and Ignat'ev, 1970; ECHA REACH Dossier: Benzoic acid; Sodemoto and Enomoto, 1980; Lemini et al., 1995; Kimmel et al., 1971; Ashby et al., 1997; Bedford and Clarke, 1971; Benton et al., 1955; Schafer and Bowles, 1985; Dawson et al., 1996; Nishihara et al., 2000; Picard et al., 2001; Kolle et al., 2010; Minor and Becker, 1971; Verrett et al., 1980; Daston et al., 1995; Peterka et al., 1986; Okubo and Kano, 2003; CIR, 2006; WHO, 1996; Lacroix et al., 2002; Kutzman et al., 1980, 1978; Bray et al., 1951; Laham et al., 1988; Laham and Potvin, 1987; Smith and Packer, 1972; Walkenstein and Weinhouse, 1953; Sherwin and Crowdle, 1922; Chidgey and Caldwell, 1986.

Literature Search and Risk Assessment Completed on: 05/30/14.

10.1.7. Skin sensitization

Based on the available data, summarized in the current IFRA Standard, benzyl alcohol is considered to be a weak skin sensitizer with a defined NESIL of 5900 μg/cm^2.

10.1.8. Risk assessment

Based on the available data, summarized in the current IFRA Standard, benzyl alcohol is considered to be a weak skin sensitizer with a defined NESIL of 5900 μg/cm2 (Table 1). The application of the Quantitative Risk Assessment (QRA) described by Api et al. (2008) results in the acceptable exposure limits summarized in Table 2. Benzyl alcohol is not predicted to be directly reactive to skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In *in chemico* experimental studies, 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 test methods. Additionally, benzyl alcohol has been evaluated in the murine local lymph node assay (LLNA). In the LLNA, benzyl alcohol was reported to have an EC3 value > 50% (12,500 μg/cm2) (RIFM, 2005a; Kashima et al., 1993a and Kashima et al., 1993b; Klecak et al., 1977, 1979, 1985; Hausen et al., 1995; Hausen et al., 1992; Ishihara et al., 1986; Sharp, 1978). The dermal sensitization potential of benzyl alcohol has been evaluated in the Human Repeated Insult Patch Test (HRIPT) and the human maximization test (HMAX). The No Observed Effect Level (NOEL) in the HRIPT is 5906 μg/cm^2 and the Lowest Observed Effect Level (LOEL) is 8858 μg/cm^2 in ethanol contacting vehicles. In the HMAX a NOEL of 6897 μg/cm^2 has been reported (RIFM, 2004a; RIFM, 1979a; RIFM, 1970; RIFM, 2002; RIFM, 2003; RIFM, 2004b; RIFM, 2005b).

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/06/14.

10.1.9. Phototoxicity/photoallergenicity

Based on the available UV spectra, benzyl alcohol does not present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

Based on the available UV spectra, benzyl alcohol does not present a concern for phototoxicity or photoallergenicity. The molar absorption coefficient for λ max between 290 and 700 nm is well below the benchmark (1000 L mol^{-1} cm^{-1}) of concern for phototoxicity and photoallergenicity (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/06/14.

10.1.11. Local respiratory toxicity

	Local respiratory toxicity
Step 1: Data	Sufficient
Step 2: *in vitro*/in silico/read across	Choose Value
Step 3: TTC* (1.4 mg/day)	Choose Value
Step 4: Generate Data	Enter Value
NOAEC	1072 mg/m^3
Margin of Exposure	170,850

*Carthew et al., 2009; #57336.

The margin of exposure for Benzyl alcohol is adequate for the respiratory endpoint at the current level of use.

10.1.12. 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. Specifically, the NOAEC for benzyl alcohol was determined to be 1072 mg/m^3 in a 2 week acute inhalation study (RIFM, 2009). There were no test substance-related macroscopic or microscopic findings.

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 (MV) of 0.17 L/min for a Sprague–Dawley rat X duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- (1.072 mg/L) (61.2 L/d) = 65.60 mg/d
- (65.6 mg/d)/(0.0016 kg lung weight of rat*) = 41,004 mg/kg lw/day

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 1.65%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) the combined inhalation exposure would be 0.153 mg/day as calculated based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual using RIFM's 2-Box/MPPD *in silico* models. To compare this estimated exposure with the Roper 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, 0.24 mg/kg lung weight/day resulting in a MOE of 170,850 (i.e., [41,004 mg/kg lw/day]/[0.24 mg/kg lung weight/day]).

The MOE is greater than 100. The material exposure by inhalation at 1.65% in a combination of the products noted above 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, 1949; Smyth, 1951; DeGaulejac, 1938; Buchbauer, 1993, 1992; Reynolds, 1995; Johnson, 2005; RIFM, 2001.

Literature Search and Risk Assessment Completed on: 06/06/14.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of benzyl 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 (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). Following the RIFM Environmental Framework, benzyl alcohol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify benzyl alcohol as either being possibly persistent nor bioaccumulative based on its structure and physical–chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical–chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

10.2.2. Risk assessment

Based on current VoU (as of 2011), benzyl alcohol presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 1993**:** The ready and ultimate biodegradability of the test material was evaluated using the sealed vessel test following the OECD 301B guideline. The source of the inoculum was secondary effluent from an unacclimatised activated sludge plant. The duration was 28 days. Benzyl alcohol achieved 95.8% biodegradation in 28 days.

RIFM, 1997**:** Benzyl alcohol was used as positive control in inherent biodegradability test according to the OECD 301B method using an acclimatized inoculum from a modified Semi-Continuous Activated Sludge (SCAS) test. Benzyl alcohol underwent 94.9% biodegradation.

10.2.3.2. Ecotoxicity. **Mattson et al. (1976):** A 96 h acute LC50 was evaluated in Fathead minnows (*Pimephales promelas*). The 96 h LC50 for benzyl alcohol in fathead minnows was 460 mg/L.

10.2.4. Other available data

Benzyl alcohol has been registered under REACH and the following additional data is available (REACH dossier; accessed on 05/23/2014).

The 96 h toxicity of benzyl alcohol to fish (*P. promelas*) was assessed in a static-acute toxicity test. Lake Superior water served as test medium. The LC50 after 96 h exposure was determined to be 460 mg/L (nominal concentration).

The toxicity of benzyl alcohol to *Daphnia magna* was assessed in a 48 h acute immobilization test according to the OECD Guideline 202. The EC50 was determined to be 230 mg/L.

The toxicity of benzyl alcohol to *D. magna* was assessed in a 21 day reproduction test according to the OECD Guideline 211. The EC50 and the NOEC for reproduction were determined to be 66 and 51 mg/L, respectively.

The toxicity of benzyl alcohol to algae was assessed in a 72 h growth inhibition test according to the OECD Guideline 201. The EC50 and NOEC for growth were determined to be 700 and 310 mg/L, respectively. The EC50 and NOEC for the area under the growth curve determined to be 500 and 310 mg/L, respectively.

10.2.5. Risk assessment refinement

Since Benzyl alcohol passed the level 2 Screening Criteria, measured data (including REACH) is included in the 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)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	921.2 mg/l			1,000,000	0.9212 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	213.8 mg/l	157.7 mg/l	48.31 mg/l	10,000	4.831 μg/l	Benzyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	601.0 mg/l	313.3 mg/l	163.9 mg/l			Neutral Organics SAR (baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.08	1.08
Biodegradation factor used	1	1
Dilution factor	3	3
Regional volume of use tonnage band	100–1000	100–1000
Risk characterization: PEC/PNEC	<1	<1

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

The RIFM PNEC is 4.831 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 06/02/14.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

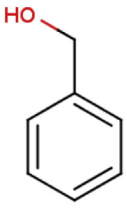
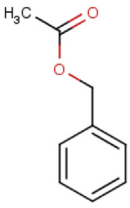
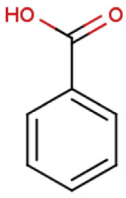
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2015.09.005.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.09.005.

Appendix

	Target material	Read across material	
Principal name	Benzyl alcohol	Benzyl acetate	Benzoic acid
CAS no.	100-51-6	140-11-4	65-85-0
Structure			
3D structure	http://www.thegoodscentscompany.com/opl/100-51-6.html	http://www.thegoodscentscompany.com/opl/140-11-4.html	http://www.thegoodscentscompany.com/opl/65-85-0.html
Read-across endpoint		•Devel/Repro	•Devel/Repro
Molecular formula	C_7H_8O	$C_9H_{10}O_2$	$C_7H_6O_2$
Molecular weight	108.14	150.18	122.12
Melting point (°C, EPISUITE)	−5.43	−0.50	48.85
Boiling point (°C, EPISUITE)	205.65	215.57	249.51
Vapor pressure (Pa @ 25 °C, EPISUITE)	7.133	24.93	0.3973
Log Kow (KOWWIN v1.68 in EPISUITE)	1.08	2.08	1.87
Water solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	4.105e+004	1605	2493
J_{max} (mg/cm^2/h, SAM)	978.9489605	85.35037463	585.5878938
Henry's Law (Pa·m^3/mol, bond method, EPISUITE)	0.022028	1.433749	0.010984
Similarity (Tanimoto score)		NA[1]	NA[2]
Developmental and Reproductive Toxicity			
ER binding (OECD)	Non binder, without OH or NH_2 group	Non binder, without OH or NH_2 group	Non binder, without OH or NH_2 group
Developmental toxicity model (CAESAR v2.1.6)	Toxicant (low reliability)	Toxicant (moderate reliability)	Toxicant (low reliability)
Rat liver S9 metabolism simulator (OECD)	See Supplemental data 1	See Supplemental data 2	No Metabolite Found

[1] The major metabolite is the target.
[2] The metabolite of the target.

Summary

There are insufficient toxicity data on Benzyl alcohol (RIFM # 107, CAS # 100-51-6). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on metabolism and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- ER binding was 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)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/rationale

- Benzyl acetate (analog) was used as a read-across analog for benzyl alcohol (target) based on:
  - The major metabolite of the analog is the target.
  - The analog is the acetate form of the target. Acetate is predicted to be readily metabolized to the corresponding alcohol and acid, therefore, the toxicity profile is expected to be the parent.
  - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular

initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - As per the OECD Toolbox, the analog is predicted to be hydrolyzed to the target (metabolite # 1).
- Benzoic acid (analog) was used as a read-across analog for benzyl alcohol (target) based on:
  - The analog is the major metabolite of the target.
  - The analog is predicted to be the oxidized products of the target. Therefore, the toxicity profile is expected to be the analog.
  - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - As per the OECD Toolbox, the target is predicted to metabolize to the analog (metabolite # 2).

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