Food and Chemical Toxicology 115 (2018) S96–S106

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment benzyl 2,2-dimethylpropanoate, CAS Registry Number 2094-69-1

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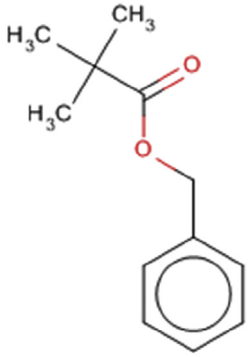
Version: 091117. This version replaces any previous versions.
Name: Benzyl 2,2-dimethylpropanoate
CAS Registry Number: 2094-69-1



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https://doi.org/10.1016/j.fct.2017.12.048
Received 3 October 2017; Received in revised form 14 December 2017; Accepted 22 December 2017
Available online 28 December 2017

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; Safford et al., 2015; Safford et al., 2017; Comiskey 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
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
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
Statistically Significant - statistically significant difference in reported results as compared to controls with a $p < .05$ using appropriate statistical test.
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

The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits 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 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 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

The material (benzyl 2,2-dimethylpropanoate) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the read across analog benzyl propionate (CAS # 140-11-4) show that benzyl 2,2-dimethylpropanoate is not genotoxic. The skin sensitization endpoint was completed by utilizing the non-reactive DST. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using benzyl acetate (CAS # 140-11-4) as a read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra and data on benzyl 2,2-dimethylpropanoate. The environmental endpoints were evaluated, benzyl 2,2-dimethylpropanoate 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 genotoxic. (Tennant et al., 1987; Shelby et al., 1993)

Repeated Dose Toxicity: NOAEL = 260 mg/kg/day. (NTP, 1993)

Developmental Toxicity: NOAEL = 100 mg/kg/day; **Reproductive Toxicity**: NOAEL = 460 mg/kg/day. (NTP, 1993)

Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1981)

Local Respiratory Toxicity: NOAEC = 61.4 mg/m^3. (RIFM, 2013a)
Environmental Safety Assessment
Hazard Assessment:
Persistence: Screening Level: 2.7 (Biowin 3) (US EPA, 2012a)
Bioaccumulation: Screening Level: 86 L/kg (US EPA, 2012a)
Ecotoxicity: Screening Level: Fish LC50: 14.49 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: 14.49 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.01449 μg/L
- **Revised PEC/PNECs (2011 IFRA Volume of Use)**: North America and Europe: Not Applicable; Cleared at screening level

1. Identification

1. **Chemical Name**: Benzyl 2,2-dimethylpropanoate
2. **CAS Registry Number**: 2094-69-1
3. **Synonyms**: Propanoic acid, 2,2-dimethyl-, phenylmethyl ester; アルカン酸（C = 1 ~ 6）ベンジル; アルキル（C = 1 ~ 5）カルボン酸フェニルアルキル（C = 1 ~ 6）; Benzyl pivalate; Benzyl 2,2-dimethylpropanoate
4. **Molecular Formula**: $C_{12}H_{16}O_2$
5. **Molecular Weight**: 192.26
6. **RIFM Number**: 6406

2. Physical data

1. **Boiling Point**: 252.16 °C (US EPA, 2012a)
2. **Flash Point**: 95 °C [GHS]
3. **Log K_{OW}**: 3.44 (US EPA, 2012a)
4. **Melting Point**: 28.29 °C (US EPA, 2012a)
5. **Water Solubility:** 54.93 mg/L (US EPA, 2012a)
6. **Specific Gravity**: Not Available
7. **Vapor Pressure:** 0.0128 mmHg @ 20 °C (US EPA, 2012a 4.0), 0.0223 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** A colorless, clear liquid with a medium floral, herbal, chamomile odor.*

*http://www.thegoodscentscompany.com/data/rw1412451.html#toorgano, retrieved 5/27/2017.

3. Exposure

1. **Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.013% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.000072 mg/kg/day or 0.0048 mg/day (RIFM, 2014)
4. **Total Systemic Exposure **:** 0.00048 mg/kg/day (RIFM, 2014)

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

4. Derivation of systemic absorption

1. **Dermal**: 100%
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. **Analogues Selected**:
   a. **Genotoxicity:** Benzyl acetate (CAS # 140-11-4)
   b. **Repeated Dose Toxicity:** Benzyl acetate (CAS # 140-11-4)
   c. **Developmental and Reproductive Toxicity**: Benzyl acetate (CAS# 140-11-4)
   d. **Skin Sensitization**: None
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity:** Benzyl acetate (CAS # 140-11-4)
   g. **Environmental Toxicity**: None
3. **Read across Justification**: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Benzyl 2,2-dimethylpropanoate 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 that 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

None.

9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 09/01/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, benzyl 2,2-dimethylpropanoate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Benzyl 2,2-dimethylpropanoate was tested in the BlueScreen assay and found to be negative for both cytotoxicity and genotoxicity in the presence and absence of metabolic activation (RIFM, 2013b). There are no studies assessing the mutagenicity of benzyl 2,2-dimethylpropanoate. The mutagenic potential of read across material benzyl acetate (CAS # 140-11-4; see Section 5) was assessed by an Ames test similar to OECD TG 471 using the plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to benzyl acetate in DMSO (dimethyl sulfoxide) at concentrations up to 10 mg per plate in the presence and absence of liver S9 fractions. No substantial increases in revertant colonies were seen with benzyl acetate with or without S9 metabolic activation (Tennant et al., 1987). The study concluded that benzyl acetate is not mutagenic under the conditions of this test.

There are no studies assessing the clastogenicity of benzyl 2, 2-dimethylpropanoate. The read across material benzyl acetate (CAS # 140-11-4; see Section 5) was identified as a read across analog. The clastogenic activity of benzyl acetate was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance or equivalent with OECD TG 474. The test material was administered via intraperitoneal injection, to groups of male and female B6C3F1 mice (5–7/sex/dose). Doses of 312, 625, or 1250 mg/kg were administered. Mice from each dose level were euthanized at 48 h after third treatment, the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (Shelby et al., 1993). Under the conditions of the study, benzyll acetate was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, benzyl acetate does not present a concern for genotoxic potential and this can be applied to benzyl 2, 2-dimethylpropanoate.

Additional References: NTP, 1993; Florin et al., 1980; Mortelmans et al., 1986; Yoo, 1986; Caspary et al., 1988; Galloway et al., 1987; Rudd et al., 1983; Rogan et al., 1986; McGregor et al., 1988; Schunk et al., 1986; Longnecker et al., 1990; Elmore and Fitzgerald, 1990; Mirsalis et al., 1989; Mirsalis et al., 1983; Foureman et al., 1994; Steinmetz and Mirsalis, 1984; Yoshikawa, 1996; Matsuoka et al., 1996; Miyagawa et al., 1995; Mitchell and Caspary, 1987; Zimmermann et al., 1989; Honma et al., 1999; Kevekordes et al., 1999, 2001; Rossman et al., 1991; Witt et al., 2000; Sasaki et al., 2000; Sekihashi et al., 2002; Yasunaga et al., 2004; Oda et al., 1978; Scott et al., 2007; Demir et al., 2010.

Literature Search and Risk Assessment Completed on : 2/12/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for benzyl 2,2-dimethylpropanoate 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 benzyl 2,2-dimethylpropanoate. Read across material, benzyl acetate (CAS # 140-11-4; see Section 5) has sufficient repeated dose toxicity data. Groups of 10 F344/N rats/sex were fed diets containing benzyl acetate at doses of 0, 3130, 6250, 12500, 25000 or 50000 ppm equivalent to 0, 230, 460, 900, 1750 or 3900 mg/kg/day for males and 0, 240, 480, 930, 1870 or 4500 mg/kg/day for females for 13 weeks. Mortality was reported among high dose group animals. Body weight gain and final body weights for the animals of the 25000 ppm dose group males were significantly lower than the control. There was a reduction in food consumption reported among 25000 ppm and 50000 ppm males and the 50000 ppm females; this was attributed to the palatability of the test material and not considered an adverse effect. Tremors and ataxia were reported among high dose group animals. Test material related lesions were reported in the brain, kidney, tongue and skeletal muscles of the thigh. Necrosis of the brain involving the cerebellum and/or the hippocampus, degeneration and regeneration of the renal tubule epithelium and degeneration and sarcolemma nuclear hyperplasia of the tongue and skeletal muscles were reported in most high dose animals. There were no alterations reported among animals treated with 12500 ppm or lower dose groups, thus the NOAEL was considered to be 12500 ppm or 900 mg/kg/day for males and 930 mg/kg/day for females (NTP, 1993). In another study, groups of ten B6C3F1 mice/sex were fed diets containing benzyl acetate at doses of 0, 3,130, 6250, 12500, 25000 or 50000 ppm equivalent to 0, 425, 1000, 2000, 3700 or 7900 mg/kg/day for males and 0, 650, 1280, 2980, 4300 or 9400 mg/kg/day for females for 13 weeks. Mortality was reported among the high dose group animals. Body weight gains and final body weights (8–31% lower among males and 12–33% lower among females) among treated animals were significantly lower than the control. Feed consumption among males of the 3100 ppm males and all treated females was lower than the control. Alterations in organ weights were reported among treated animals. However, this was attributed to lower body weight in relation to lower food consumption and therefore, it was difficult to make comparisons. Tremors were reported among females of the 12500 ppm and higher dose groups. Necrosis of the brain involving the hippocampus was reported among animals of the high dose groups. Hepatocellular necrosis was reported among one high dose male and was characterized as moderate severity necrosis of the hepatocytes randomly distributed throughout the hepatic lobules. No other test material related alterations were reported among animals of the 6250 ppm or lower dose groups. Due to reduction in body weights and body weight gains among all treated animals in conjunction with reduced food consumption, a NOAEL could not be derived from the study conducted on mice (NTP, 1993). Later, A dietary 2-year chronic toxicity study was conducted in F344/N rats. Groups of 60 rats/sex/dose were fed diets containing 0, 3000, 6000, or 12000 ppm benzyl acetate (average daily consumption level of 0, 130, 260, or 510 mg/kg/day for males and 0, 145, 290, or 575 mg/kg/day for females) for 2 years. High dose males and all exposed females had lower mean body weights than controls. Feed consumption was slightly reduced in high dose males; there were no differences in feed consumption in females. Food consumption among the high dose males was lower than the control. There were no clinical findings reported among treated animals. Thus, the NOAEL for males and females was considered to be 6000 ppm based on lower body weight at higher doses (NTP, 1993). In another study, groups of 60 male and female B6C3F1 mice were fed benzyl acetate in the diet at concentrations of 0, 330, 1000 or 3000 ppm equivalent to 0, 35, 110, or 345 mg/kg/day for males and 0, 40, 130, or 375 for females. The high dose female mice showed a statistically significant increase in survival. The mean body weights of treated mice were significantly lower (2–14%) than the controls except for the 330 ppm groups. There was no significant difference in terms of food consumption among treated and control group mice. In the 2-year NTP study with mice (NTP, 1993), benzyl acetate administration in the food of female and male mice was associated with a dose related increase in the incidence or severity of non-neoplastic nasal lesions (i.e., mucosal atrophy and degeneration, cystic hyperplasia of the submucosal gland, and luminal exudates and pigmentation of the mucosal epithelium). The study stated that although the nose was not the deposition site for benzyl acetate, nasal tissue could have been exposed directly to high concentrations of the chemical or its degradation products (NTP, 1993). Thus, it was concluded that there was no evidence of carcinogenic

activity among animals treated with benzyl acetate via diet. Overall, the most conservative NOAEL of 6000 ppm or 260 mg/kg/day derived from the 2-year chronic study conducted on rats was considered.

Therefore, the benzyl 2,2-dimethylpropanoate MOE for the repeated dose toxicity endpoint can be calculated by dividing the benzyl acetate NOAEL in mg/kg/day by the total systemic exposure to benzyl 2,2-dimethylpropanoate, 260/0.00048 or 541667.

In addition, the total systemic exposure to benzyl 2,2-dimethylpropanoate (0.48 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: RIFM, 1986.

Literature Search and Risk Assessment Completed on: 2/24/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for benzyl 2,2-dimethylpropanoate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental data on benzyl 2,2-dimethylpropanoate. Read across material, benzyl acetate (CAS # 140-11-4; see Section 5) has sufficient developmental toxicity data. In a developmental toxicity study, groups of 20–22 pregnant rats were gavaged daily from gestation days 6–15 with 0, 10, 100, 500, or 1000 mg/kg bodyweight/day benzyl acetate in olive oil. Body weights of the live 1000 mg/kg/day male and female fetuses were significantly reduced. The number of fetuses with internal variations (dilation of the renal pelvis and dilation of lateral ventricle) were significantly increased in the 500 and 1000 mg/kg/day litters (Ishiguro et al., 1993). The number of fetuses with skeletal variations (wavy ribs, dumbbell shape of thoracic vertebra body, absence of thoracic vertebra body, splitting of thoracic vertebra body, lumbar ribs, and reduced ossification of cervical vertebra body, caudal vertebra body, and sternebrae) were significantly increased in the 1000 mg/kg/day litters. Within this dose range, benzyl acetate produced a delayed development of the fetuses at the 1000 mg/kg/day but did not produced teratogenic effects. Thus, the developmental toxicity NOAEL was considered to be 100 mg/kg/day. **Therefore, the benzyl 2,2-dimethylpropanoate MOE for the developmental toxicity endpoint can be calculated by dividing the benzyl acetate NOAEL in mg/kg/day by the total systemic exposure to benzyl 2,2-dimethylpropanoate, 100/0.00048 or 208333.**

There are no reproductive toxicity data on benzyl 2,2-dimethylpropanoate. Read across material, benzyl acetate (CAS # 140-11-4; see Section 5) has sufficient reproductive toxicity data. Groups of ten F344/N rats/sex were fed diets containing benzyl acetate at doses of 0, 3130, 6250, 12500, 25000 or 50000 ppm equivalent to 0, 230, 460, 900, 1750 or 3900 mg/kg/day for males and 0, 240, 480, 930, 1870 or 4500 mg/kg/day for females for 13 weeks. Detailed histopathological evaluations were performed on all control, 25000 and 50000 ppm dose group rats including the male (preputial, prostate, testis with epididymis and seminal vesicles) and female (ovary, preputial or clitoral glands and uterus) reproductive organs. The testis and epididymis were evaluated for males of the 6250 and 12500 ppm dose groups as well. Sperm morphology and vaginal cytology were evaluated among all control and treated rats. Results showed mild to moderate aspermatogenesis among the high dose males, atrophy of the seminiferous tubules among the 12500 and 25000 ppm dose group males. No other test material lesions were reported among the 6250 ppm or lower dose group animals. There were no test material related alterations in sperm morphology or estrous cycles reported among treated animals. Thus, the NOAEL for the reproductive toxicity was considered to be 6250 ppm, 460 or 480 mg/kg/day for males and females, respectively (NTP, 1993). Groups of ten B6C3F1 mice/sex were fed diets containing benzyl acetate at doses of 0, 3, 130, 6250, 12500, 25000 or 50000 ppm equivalent to 0, 425, 1000, 2000, 3700 or 7900 mg/kg/day for males and 0, 650, 1280, 2980, 4300 or 9400 mg/kg/day for females for 13 weeks. Detailed histopathological evaluations were performed on all control, 25000 females and all 50,000 ppm mice, including the male (preputial, prostate, testis with epididymis and seminal vesicles) and female (ovary, preputial or clitoral glands and uterus) reproductive organs. Sperm morphology and vaginal cytology were evaluated among all control and treated mice. No test material related alterations were reported among the male and female reproductive organs of the treated animals. No chemical-related effects on sperm morphology were reported among treated animals. A significant dose-related decrease in body weight and significant lengthening of the estrous cycle was reported among female mice. The lengthening of the estrous cycle was reported to be related to significant decrease in body weights (~30%) and food consumption and, hence was not considered to be an adverse effect. Thus, the NOAEL was considered to be 50000 ppm or 7900 or 9400 mg/kg/day for males and females respectively (NTP, 1993). The most conservative NOAEL of 460 mg/kg/day was considered from the 13-week study conducted on rats for the reproductive toxicity endpoint. **Therefore, the benzyl 2,2-dimethylpropanoate MOE for the reproductive toxicity endpoint can be calculated by dividing the benzyl acetate NOAEL in mg/kg/day by the total systemic exposure to benzyl 2,2-dimethylpropanoate, 460/0.00048 or 958333.**

In addition, the total systemic exposure to benzyl 2,2-dimethylpropanoate (0.48 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: RIFM, 1986.

Literature Search and Risk Assessment Completed on: 2/24/2017.

10.1.4. Skin sensitization

Based on the limited existing data and application of DST, benzyl 2,2-dimethylpropanoate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization data are available for benzyl 2, 2-dimethylpropanoate. Based on the available data and application of DST, benzyl 2,2-dimethylpropanoate does not present a concern for skin sensitization. The chemical structure of this material indicates that it could possibly react with proteins, although little or no reaction would likely occur under physiological conditions (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). A sensitization reaction was observed when benzyl 2,2-dimethylpropanoate was tested in a human repeated insult patch test which was not confirmed upon rechallenge (RIFM, 1981). Acting conservatively, due to inconclusive data, current exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2. The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentration for benzyl 2,2-dimethylpropanoate which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: RIFM, 1962; Klecak, 1979, 1985; Ishihara et al., 1986; Greif, 1967; RIFM, 1988a; RIFM, 1988b; RIFM, 1988c; RIFM, 1975e; RIFM, 1975d; RIFM, 1975c; RIFM, 1975b; RIFM, 1975a; RIFM, 1961.

Literature Search and Risk Assessment Completed on: 02/24/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and human study data, benzyl 2,2-dimethylpropanoate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al.,

Table 1
Acceptable concentrations for benzyl 2, 2-dimethylpropanoate based on non-reactive DST–.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in finished products	95th Percentile Concentration
1	Products applied to the lips	0.069%	0.00%
2	Products applied to the axillae	0.021%	0.00%[b]
3	Products applied to the face using finger tips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.01%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.01%
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	0.00%
9	Products with body and hand exposure, primarily rinse off	0.75%	0.00%[b]
10	Household care products with mostly hand contact	2.70%	0.01%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.46%

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).

2009). In a photo-HRIPT, a solution of 10% benzyl 2,2-dimethylpropanoate in white petrolatum did not result in either phototoxic or photoallergenic reactions (RIFM, 1981). Based on lack of absorbance and the human data, benzyl 2,2-dimethylpropanoate would not be expected to present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 04/14/17.

10.1.6. Local respiratory toxicity

There are no inhalation data available on benzyl 2,2-dimethylpropanoate; however, in a 2-week inhalation study for the analog benzyl acetate (CAS # 140-11-4; see Section 5), a NOAEC of 61.4 mg/m^3 is reported by RIFM (2013a).

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 2-week study conducted in rats with nose-only inhalation exposure, a NOAEC of 614 mg/m^3 was reported for benzyl acetate (RIFM, 2013a). Test substance-related higher levels of lactate dehydrogenase were noted in the bronchoalveolar lavage fluid. Although the authors did not consider these effects as adverse, for the purpose of estimating local respiratory toxicity MOE, a NOAEC of 61.4 mg/m^3 (the mid dose given) was considered.

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

- (61.4 mg/m^3)/(1m^3/1000 L) = 0.0614 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/day
- (0.0614 mg/L) (61.2 L/day) = 3.76 mg/day
- (3.76 mg/day)/(0.0016 kg lung weight of rat*) = 2350 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0048 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, 2017 and 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 0.0074 mg/kg lung weight/day resulting in a MOE of 317568 (i.e., [2350 mg/kg lung weight/day]/[0.0074 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 0.0048 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: RIFM, 1977; RIFM, 1997b; Silver, 1992; RIFM, 1997a; Isola et al., 2003b; RIFM, 2003a; Rogers et al., 2003; RIFM, 2003b; Isola et al., 2003a; Isola et al., 2004b; Smith et al., 2004; RIFM, 2004; Isola et al., 2004a; Rogers et al., 2005; Randazzo et al., 2014; Vethanayagam et al., 2013

Literature Search and Risk Assessment Completed on: 07/24/17

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of benzyl 2,2-dimethylpropanoate 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; US EPA, 2012b) 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, benzyl 2,2-dimethylpropanoate 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 benzyl 2,2-dimethylpropanoate 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 EPI Suite v4.11).

10.2.2. Risk assessment

Based on current Volume of Use (2011), benzyl 2,2-dimethylpropanoate does not present a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.3. Other available data

Benzyl 2,2-dimethylpropanoate has been pre-registered for REACH with no additional data at this time.

10.2.4. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level (**Tier 1)**	14.49 mg/L			1,000,000	0.01449 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.44	3.44
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.01449 μg/L. The revised PEC/PNECs for EU and NA: Not available; cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 8/10/15.

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.2017.12.048.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.12.048.

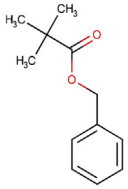
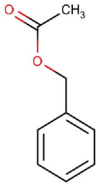
Appendix

Read across justification

Methods:

The read across analogs were identified following the strategy for structuring and reporting a read across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was examined. Third, appropriate read across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical-chemical properties of the target substance and the read across analogs were calculated using EPI Suite™ v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target material	Read across material
Principal Name	Benzyl 2,2-dimethylpropanoate	Benzyl acetate
CAS No.	2094-69-1	140-11-4
Structure		
Similarity (Tanimoto score)		0.71
Read across endpoint		• Repeated Dose • Reproductive and Developmental Toxicity • Genotoxicity • Respiratory
Molecular Formula	$C_{12}H_{16}O_2$	$C_9H_{10}O_2$
Molecular Weight	192.26	150.18
Melting Point (°C, EPISUITE)	28.29	−0.50
Boiling Point (°C, EPISUITE)	252.16	215.57
Vapor Pressure (Pa @ 25°C, EPISUITE)	2.97	25
Log Kow (KOWWIN v1.68 in EPISUITE)	3.44	1.96
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	54.93	3100
J_{max} (mg/cm^2/h, SAM)	3.51	64.03
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	3.36E + 000	1.43E + 000
Genotoxicity		
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• AN2-Shiff base formation after aldehyde release • SN1-Nucleophilic attach after carbenium ion formation • SN2-Acylation-Specific acetate esters • SN2-Nuceophilic substitution at sp3 carbon atom
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition	• Michael addition • P450 Mediated activation to Quinone and Quinone type chemicals
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non-carcinogen (good reliability)	• Non-carcinogen (Experimental value)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, without OH or NH_2 group	• Non-binder, without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)	• Toxicant (moderate reliability)
Skin Sensitization		
Protein binding by OASIS v1.4		• SN2 reaction at a sp3 carbon atom

	• SN2 reaction at a sp3 carbon atom	
	• Activated alkyl esters and thioesters	• Activated alkyl esters and thioesters
Protein binding by OECD	• SN2 reaction at a sp3 carbon atom	• SN2 reaction at a sp3 carbon atom
	• Allyl acetates and related chemicals	• Allyl acetates and related chemicals
Protein binding potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein binding alerts for skin sensitization by OASIS v1.4	• SN2 reaction at a sp3 carbon atom	• SN2 reaction at a sp3 carbon atom
	• Activated alkyl esters and thioesters	• Activated alkyl esters and thioesters
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (moderate reliability)	• Sensitizer (moderate reliability)
Respiratory		
Respiratory sensitization OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See supplemental data 1	See supplemental data 2, 3 and 4

1 NA[a] Major metabolites or analog of major metabolites of the target substance.
2 Patel et al., 2002.
3 Chidgey et al., 1987.
4 McMahon et al., 1989.

Summary:

There are insufficient toxicity data on the target material benzyl 2,2-dimethylpropanoate (CAS # 2094-69-1). Hence, *in silico* evaluation was conducted to determine a read across analog for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, benzyl acetate (CAS # 140-11-4) was identified as a read across material with data for its respective toxicological endpoints.

Conclusion/Rationale:

- For the target material benzyl 2,2-dimethylpropanoate (CAS # 2094-69-1), benzyl acetate (CAS # 140-11-4) was used as a read across analog for the genotoxicity, developmental and reproductive, repeated dose and local respiratory toxicity endpoints.
  - o The target substance and the read across analog are structurally similar and belong to the structural class of esters of primary aryl alcohols.
  - o The target substance and the read across analog share an esterified primary aryl alcohol structure.
  - o The key difference between the target substance and the read across analog is in the aliphatic acid component of the ester. The target has a branched chain acid whereas the read across analog has a straight chain acid. This structural difference between the target substance and the read across analog does not affect consideration of the toxicological endpoints.
  - o Similarity between the target substance and the read across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicoloigcal endpoint.
  - o The physical-chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target substance and the read across analog.
  - o The target substance and the read across analog benzyl acetate are predicted to be toxicants by the CAESAR model for developmental toxicity. ER binding alert is negative for both of the substances. Data described in the developmental toxicity section above show that the margin of exposure for the read across analog is adequate at the current level of use. Therefore, the alert is superseded by the available data.
  - o The target substance and the read across analog benzyl acetate has a protein binding alert by OASIS and OECD QSAR Toolbox. Also, according to the CAESAR model, both of these substances are predicted to be sensitizers. These alerts show similar or comparable reactivity between the read across analog and the target substance. The data described in the skin sensitization section above show that the read across analog, benzyl acetate, does not pose a concern for the skin sensitization endpoint. Therefore, the alerts are superseded by the available data.
  - o The target substance and the read across analog are expected to be metabolized similarly as shown by the metabolism simulator.

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