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Update to RIFM fragrance ingredient safety assessment, benzyl acetate, CAS Registry Number 140-11-4

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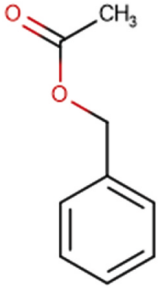
Name: Benzyl acetate CAS Registry Number: 140-11-4



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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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
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.,

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

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api 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.

Benzyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that benzyl acetate is not genotoxic, provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints, and show that there are no safety concerns for benzyl acetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; benzyl acetate is not phototoxic/photoallergenic. The environmental endpoints were evaluated; benzyl acetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	NTP (1993)
Repeated Dose Toxicity: NOAEL = 260 mg/kg/day.	NTP (1993)
Reproductive Toxicity: Developmental NOAEL = 100 mg/kg/day; Fertility NOAEL = 460 mg/kg/day.	(Ishiguro et al., 1993; NTP, 1993)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(RIFM, 1985b; RIFM, 1986; RIFM, 1987; RIFM, 1988a)
Phototoxicity/Photoallergenicity: Not phototoxic/ not expected to be photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1983)
Local Respiratory Toxicity: NOAEC = 61.4 mg/m^3 or 10 ppm.	RIFM (2013)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical Measured Value: 99.7% (OECD 301B)	RIFM (1994b)
Bioaccumulation:	
Screening-level: 9.12 L/Kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 28-day fish chronic NOEC: 0.92 mg/L	(Holcombe et al., 1995)
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: 28-day fish chronic NOEC: 0.92 mg/L	(Holcombe et al., 1995)
RIFM PNEC is: 18.4 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1	

1. Identification

1. **Chemical Name:** Benzyl acetate
2. **CAS Registry Number:** 140-11-4
3. **Synonyms:** Acetic acid, phenylmethyl ester; Benteine; Benzyl ethanoate; Methyl α-toluate; Methyl phenylethanoate; Methyl benzeneacetate; Acetic acid, benzyl ester; Phenylmethyl acetate; ｱﾙｶﾝ酸(C = 1 ~ 6)ﾍﾞﾝｼﾞﾙ; ｱﾙｷﾙ(C = 1 ~ 5)ｶﾙﾎﾞﾝ酸ﾌｪﾆﾙｱﾙｷﾙ(C = 1 ~ 6); Benzyl acetate
4. **Molecular Formula:** $C_9H_{10}O_2$
5. **Molecular Weight:** 150.17 g/mol
6. **RIFM Number:** 106
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 216 °C (Fragrance Materials Association [FMA]), 215.57 °C (EPI Suite)
2. **Flash Point:** 195 °F; CC (FMA), 102 °C (Globally Harmonized System)
3. **Log K_{OW}:** 2.0 at 35 °C (RIFM, 2004d), 2.08 (EPI Suite)
4. **Melting Point**: -0.5 °C (EPI Suite)
5. **Water Solubility:** 1605 mg/L (EPI Suite)
6. **Specific Gravity:** 1.06 g/mL (RIFM, 1994b), 1.054–1.058 (FMA), 1.052–1.056 (FMA)

7. **Vapor Pressure:** 0.125 mm Hg at 20 °C (EPI Suite v4.0), 0.1 mm Hg 20 °C (FMA), 0.187 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless to very pale yellow liquid having a characteristic floral odor

3. Volume of use (Worldwide band)

1. >1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.048% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0036 mg/kg/day or 0.26 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.015 mg/kg/day (RIFM, 2019)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford, 2015, 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** 78.7%

Bronaugh et al., 1990: The skin absorption of [7–^{14}C] benzyl acetate 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 the abdominal skin for 24 h. Urine was collected for an additional 4 days. The extent of dermal absorption was estimated from the number 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 acetate was 17.3% ± 2.7% and 78.7% ± 7.5%, respectively. When the site was not occluded, the absorption was 34.6% ± 9.4%.

2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low.

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

None.

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

Benzyl acetate is reported to occur in the following foods by the VCF*:

Camomile.
Capers (*Capparis spinoza*).
Cloves (*Eugenia caryophyllata* Thunberg).
Hog plum (*Spondias mombins* L.)
Melon.
Passion fruit (*Passiflora* species).
Plum (*Prunus* species).
Tea.
Vanilla.
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. This is a partial list.

9. REACH dossier

Available; accessed 06/16/21 (ECHA, 2011).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, benzyl acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Benzyl acetate was negative in several Ames assays conducted by the National Toxicology Program (NTP) using guidelines similar to OECD 471 using the modified preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98, and TA100 were tested with benzyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 10000 μg/plate in the presence and absence of metabolic activation. No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation (NTP, 1993). Under the conditions of the test, benzyl acetate was considered negative in the Ames test.

Benzyl acetate was assessed for clastogenic activity in an *in vitro* chromosome aberration study. Benzyl acetate did not induce chromosome damage in Chinese hamster ovary cells with and without metabolic activation at concentrations up to 5000 μg/mL (Tennant et al., 1987). Several *in vivo* studies assessing the effects of benzyl acetate in

chromosomal aberrations and unscheduled DNA synthesis assays demonstrated a lack of genotoxic potential (NTP, 1993; Steinmetz and Mirsalis, 1984). In a study performed by the NTP, B6C3F1 mice were administered daily intraperitoneal injections of benzyl acetate in corn oil for 3 days at doses of 0, 312.5, 625, and 1250 mg/kg. The animals were euthanized 24 h following the last injection, and bone marrow was assessed for the induction of micronucleated polychromatic erythrocytes. No significant increase in the frequency of micronucleated erythrocytes was observed (NTP, 1993). Under the conditions of the study, benzyl acetate was considered negative for chromosome damage in the *in vivo* micronucleus assay.

Based on the available data, benzyl acetate does not present a concern for genotoxic potential.

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; Rossman et al., 1991; Witt et al., 2000; Sasaki et al., 2000; Brewer and Colditz, 1999; Kevekordes et al., 2001; 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: 06/04/21.

11.1.2. Repeated dose toxicity

The MOE for benzyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on benzyl acetate. 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. Bodyweight 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 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 the 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 of the high-dose animals. There were no alterations reported among the animals treated with 12500 ppm or lower doses. Thus, the NOAEL was considered to be 12500 ppm or 900 mg/kg/day for the males and 930 mg/kg/day for the females (NTP, 1993).

In another study, groups of 10 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 the males and 0, 650, 1280, 2980, 4300, or 9400 mg/kg/day for the females) for 13 weeks. Mortality was reported among the high-dose group animals. Bodyweight gains and final body weights (8%–31% lower among males and 12%–33% lower among females) among the treated animals were significantly lower than the control. Feed consumption among the males of the 3100-ppm group 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 the females of the 12500-ppm and higher dose groups. Necrosis of the brain involving the hippocampus was reported among the animals of the high-dose groups. Hepatocellular necrosis was reported among 1 high-dose male and was characterized as moderate severity necrosis of the hepatocytes randomly distributed throughout the hepatic lobules. No other treatment-related alterations were reported among the animals of the 6250-ppm or lower dose groups. Due to a reduction in body weights and bodyweight gains among all of the 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. The high-dose males and all exposed females had lower mean body weights than the controls. Feed consumption was slightly reduced in the high-dose males; there were no differences in feed consumption in the females. Food consumption among the high-dose males was lower than in the control. There were no clinical findings reported among the 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 the males and 0, 40, 130, or 375 for the 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 the treated and control group mice. In the 2-year NTP study with mice (NTP, 1993), benzyl acetate administration in the food of the 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 the 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 acetate 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 acetate, 260/0.015 or 17333.

In addition, the total systemic exposure to benzyl acetate (15 μg/kg/day) is below the TTC (30 μg/kg/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: None.

Literature Search and Risk Assessment Completed On: 05/18/21.

11.1.3. Reproductive toxicity

The MOE for benzyl acetate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on benzyl acetate. 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 body weight/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 the lateral ventricle) were significantly increased in the 500 and 1000 mg/kg/day litters. 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 1000 mg/kg/day but did not produce teratogenic effects. Thus, the developmental toxicity NOAEL was considered to be 100 mg/kg/day (Ishiguro et al., 1993). **Therefore, the benzyl acetate 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 acetate, 100/0.015 or 6667.**

There are sufficient fertility data on benzyl acetate. 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. 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 and 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 treatment-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, or 460 or 480 mg/kg/day for males and females, respectively (NTP, 1993). Groups of 10 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 mice, 25000-ppm females, and all 50000-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 treatment-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 a significant decrease in body weights (approximately 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 2,4-dimethylbenzyl acetate MOE for the fertility endpoint can be calculated by dividing the benzyl acetate NOAEL in mg/kg/day by the total systemic exposure to 2,4-dimethylbenzyl acetate, 460/0.015 or 30667.**

In addition, the total systemic exposure to 2,4-dimethylbenzyl acetate (15 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/18/21.

11.1.4. Skin sensitization

Based on the existing data, benzyl acetate presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, benzyl acetate does not present a concern for skin sensitization. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). However, in several guinea pig test methods, no reactions indicative of sensitization were observed with benzyl acetate (RIFM, 1985b; RIFM, 1986; RIFM, 1985a; RIFM, 1985c). No sensitization reactions were observed when benzyl acetate was tested in a human maximization test (Greif, 1967). Additionally, in several Confirmation of No Induction in Humans tests (CNIHs) up to 8% (9448 μg/cm^2) of benzyl acetate in 3:1 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of skin sensitization were observed (RIFM, 1987; RIFM, 1988a; RIFM, 1975e; RIFM, 1988b; RIFM, 1988c; RIFM, 1988d; RIFM, 1975d; RIFM, 1975c; RIFM, 1975b; RIFM, 1975a).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, benzyl acetate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/18/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the existing data and available UV/Vis absorption spectra, benzyl acetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra (OECD TG 101) for benzyl acetate demonstrate no absorbance between 290 and 700 nm. In a guinea pig phototoxicity study, no reactions indicative of phototoxic responses were observed after application of 3% or 10% benzyl acetate (RIFM, 1983). Based on the existing *in vivo* data and the lack of absorbance in the critical range, benzyl acetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for benzyl acetate were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/26/21.

11.1.6. Local respiratory toxicity

The MOE for benzyl acetate is adequate for the respiratory endpoint at the current level of use.

11.1.6.1. 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 acute study conducted in rats with nose-only inhalation exposure, a NOAEC of 614 mg/m^3 was reported for benzyl acetate (RIFM, 2013). Test material-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^3/1000L) = 0.0614 mg/L

- Minute ventilation of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (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 0.26 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford, 2015). 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 0.4 mg/kg lung weight/day resulting in a MOE of 5875 (i.e., [2350 mg/kg lung weight/day]/[0.4 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 0.30 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: Troy (1977); UGCM, 1997; Silver (1992); RIFM, 1997; RIFM, 2003b; RIFM, 2003c; Rogers et al., 2003a; RIFM, 2003d; RIFM, 2003a; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Isola et al., 2004a; Rogers et al., 2005; RIFM, 2014; Vethanayagam et al., 2013.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of benzyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, benzyl acetate 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 EPI Suite v4.11 (US EPA, 2012a) did not identify benzyl acetate 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 v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), benzyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation:

RIFM, 1994b: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test according to the OECD 301B method. The biodegradation rate was 99.7% on day 28.

RIFM, 1992: Degradation of the test material was evaluated using the modified OECD screening test according to Method C.4-B. Degradation of 100% was determined after 28 days.

RIFM, 2012: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301 F guideline. Biodegradation of 85% was observed after 28 days and 92% after 54 days.

Ecotoxicity:

RIFM, 2011: A *Daphnia magna* immobilization study following OECD TG 202 was reported under flow-through conditions. The 48-h EC50 value based on the mean measured concentration was reported to be 37 mg/L.

RIFM, 1994a: A 96-h acute toxicity study was conducted with Zebrafish. The 96-h LC0 was 4.6 mg/L (arithmetic mean of analytical values); LC100: 13.7 mg/L (arithmetic mean of analytical values) and the geometric mean: LC0/LC100: 7.9 mg/L.

Holcombe et al., 1995: The 96-h LC50 of benzyl acetate in juvenile Japanese medaka (*Oryzias latipes*) fish was 4.00 mg/L, based on nominal test concentration.

Holcombe et al., 1995: A 28-day chronic study with benzyl acetate was carried out under flow-through test conditions with medaka (*Oryzias latipes*). The chronic MATC was calculated to be 1.33 mg/L. NOEC value was 0.92 mg/L.

Other available data:

Benzyl acetate has been registered for REACH, and the following additional data is available (ECHA, 2011):

The ready biodegradability of the test material was evaluated using the CO_2 evolution test according to the OECD 301B guideline. Degradation of 100.9% was observed after 28 days.

A 48-h D*aphnia magna* acute study was conducted according to the OECD 202 guidelines under semi-static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 17 mg/L.

A 72-h algae inhibition test was conducted according to the OECD 201 method under static conditions. The following EC50s were reported: 110 mg/L and 92 mg/L for growth rate and biomass, respectively. The 72-h NOEC based on the mean measured concentration was reported to be 52 mg/L. All the test results are based on the mean measured concentration.

11.2.3. Risk assessment refinement

The REACH dossier reports a PNEC of 4 μg/L, which has been calculated based on an acute study. For a more conservative approach, the PNEC in this document has been calculated based on an available chronic fish study (this study is also reported in the REACH dossier). However, both approaches result in PEC/PNEC<1.

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)**	202.5			1000000	0.2025	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	18.01	37.11	15.59	10000	1.559	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	104.36	59.70	45.86			Neutral Organics
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	4.0		0.92	50	18.4	
Daphnia		17				
Algae		92	52			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.0	2.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	>1000	>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 18.4 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 06/14/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://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 02/11/22.

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.

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