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Short Review

RIFM fragrance ingredient safety assessment, benzyl valerate, CAS Registry Number 10361-39-4

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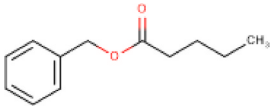
Name: Benzyl valerate
CAS Registry Number: 10,361-39-4



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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)

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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., 2015a; 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
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 valerate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog benzyl propionate (CAS # 122-63-4) show that benzyl valerate is not expected to be genotoxic. Data on read-across analog benzyl acetate (CAS # 140-11-4) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints. Data from read-across analog benzyl acetate (CAS # 140-11-4) show that there are no safety concerns for benzyl valerate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; benzyl valerate is not photoirritating/photoallergenic. The environmental endpoints were evaluated; benzyl valerate 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 (VoU) 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 expected to be genotoxic.	(RIFM, 2011; RIFM, 2001; RIFM, 2016b)
Repeated Dose Toxicity: NOAEL = 260 mg/kg/day.	NTP (1993)
Reproductive Toxicity: Developmental toxicity: 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)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic. (UV/Vis Spectra; RIFM Database)	
Local Respiratory Toxicity: NOAEC = 61.4 mg/m^3.	RIFM (2013a)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Screening-level: 3.2 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 102 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 11.62 mg/L	(RIFM Framework; Salvito, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 11.62 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.01162 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Benzyl valerate
2. **CAS Registry Number:** 10,361-39-4
3. **Synonyms:** Benzyl pentanoate; Pentanoic acid, phenylmethyl ester; Benzyl valerate
4. **Molecular Formula:** $C_{12}H_{16}O_2$
5. **Molecular Weight:** 192.25 g/mol
6. **RIFM Number:** 6226
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 269.08 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 3.55 (EPI Suite)
4. **Melting Point**: 32.02 °C (EPI Suite)
5. **Water Solubility:** 44.15 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00484 mm Hg at 20 °C (EPI Suite v4.0), 0.00859 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 liquid. Powerful fruity and somewhat musky, animal-like odor.

3. Volume of use (worldwide band)

1. <0.1 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0068% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0000014 mg/kg/day or 0.000097 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.000079 mg/kg/day (RIFM, 2019)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogs Selected:

a. **Genotoxicity:** Benzyl propionate (CAS # 122-63-4)
b. **Repeated Dose Toxicity:** Benzyl acetate (CAS # 140-11-4)
c. **Reproductive Toxicity:** Benzyl acetate (CAS # 140-11-4)
d. **Skin Sensitization:** Benzyl acetate (CAS # 140-11-4)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** Benzyl acetate (CAS # 140-11-4)
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

Benzyl valerate is reported to occur in the following foods by the VCF*:
Macadamia nut (*Macadamia integrifolia*).
Mangifera species.
Sea buckthorn (*Hippophaë rhamnoides L.*)
Turpentine oil (*Pistacia terebinthus*).
*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.

9. REACH dossier

No dossier available as of 06/15/21.

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 valerate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Benzyl valerate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of benzyl valerate; however, read-across can be made to benzyl propionate (CAS # 122-63-4; see Section VI).

The mutagenic activity of benzyl propionate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with benzyl propionate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Increases in the mean number of revertant colonies were observed in strain TA1535 in the absence of S9 (RIFM, 2001). The increases were determined to be dose-related and statistically significant. Under the conditions of the study, benzyl propionate was mutagenic in the Ames test, and this can be extended to benzyl valerate.

To further investigate the positive result observed in the Ames test, the mutagenic activity of benzyl propionate has been evaluated in a second bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strain TA1535 was treated with benzyl propionate in DMSO at concentrations up to 4000 μg/plate. A small dose-related increase in the mean number of revertant colonies was observed in the absence of S9 (RIFM, 2011). However, these increases were not statistically significant and were not considered to be biologically relevant. Under the conditions of the study, benzyl propionate was not mutagenic in the Ames test, and this can be extended to benzyl valerate.

To further confirm the lack of mutagenicity for benzyl propionate, a mammalian cell gene mutation assay (HPRT assay) was conducted according to OECD TG 476 and GLP guidelines. Chinese hamster lung cells (V79) were treated with benzyl propionate in DMSO at concentrations of 12.5, 25.0, 50.0, 100.0, 200.0, 300.0 μg/mL (as determined in a preliminary toxicity assay), for 4 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of

the test material, either with or without metabolic activation (RIFM, 2016a). Under the conditions of the study, benzyl propionate was not mutagenic to mammalian cells *in vitro*, and this can be extended to benzyl valerate.

The clastogenic activity of benzyl propionate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with benzyl propionate in DMSO at concentrations up to 1642.0 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1642.0 μg/mL in the presence and absence of metabolic activation. Benzyl propionate did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2016b). Under the conditions of the study, benzyl propionate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to benzyl valerate.

Additional References: RIFM, 2014b; Oda et al., 1978; RIFM, 2013b.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on benzyl valerate. Read-across material benzyl acetate (CAS # 140-11-4; see Section VI) 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, 12,500, 25,000, or 50,000 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 25,000 ppm dose group males were significantly lower than the control. There was a reduction in food consumption reported among 25,000 ppm and 50,000 ppm males and the 50,000 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 12,500 ppm or lower dose groups; thus, the NOAEL was considered to be 12,500 ppm or 900 mg/kg/day for males and 930 mg/kg/day for 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, 12, 500, 25,000, or 50,000 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 high-dose group animals. Bodyweight 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. Alteration in organ weights was reported among treated animals. However, this was attributed to lower body weight in relation to lower food consumption; hence it was difficult to make comparisons. Tremors were reported among females of the 12,500 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 characterized by necrosis of the hepatocytes of moderate severity randomly distributed throughout the hepatic lobules. No other treatment-related alterations were reported among animals of the 6250 ppm or lower dose groups. Due to reduction in body weights and bodyweight 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 12,000 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 in 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 (1993) with mice, 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 NTP 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 was considered, derived from the 2-year chronic study conducted on rats.

Therefore, the benzyl valerate 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 valerate, 260/0.000079, or 3291139.

In addition, the total systemic exposure to benzyl valerate (0.079 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: 05/21/21.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no developmental toxicity data on benzyl valerate. Read-across material benzyl acetate (CAS # 140-11-4; see Section VI) 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/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, dilation of 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 valerate 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 valerate, 100/0.000079, or 1265822.**

There are no fertility data on benzyl valerate. Read-across material benzyl acetate (CAS # 140-11-4; see Section VI) has sufficient fertility data. Groups of 10 F344/N rats/sex were fed diets containing benzyl acetate at doses of 0, 3130, 6250, 12,500, 25,000, or 50,000 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, 25,000 and 50,000 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 12,500 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 12,500 and 25,000 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 fertility was considered to be 6250 ppm, 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, 12,500, 25,000, or 50,000 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, 25,000 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 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 50,000 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-weeks study conducted on rats for the reproductive toxicity endpoint. **Therefore, the benzyl valerate MOE for the fertility endpoint can be calculated by dividing the benzyl acetate NOAEL in mg/kg/day by the total systemic exposure to benzyl valerate, 460/0.000079, or 5822784.**

In addition, the total systemic exposure to benzyl valerate (0.079 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: 05/21/21.

11.1.4. Skin sensitization

Based on read-across benzyl acetate (CAS # 140-11-4), benzyl valerate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. No skin sensitization data are available for benzyl valerate. Based on read-across material benzyl acetate (CAS # 140-11-4; see Section VI), benzyl valerate is not considered a sensitizer. The chemical structures of these materials indicate that they 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 read-across material, benzyl acetate (RIFM, 1985b; RIFM, 1986; RIFM, 1985a; RIFM, 1985c). Additionally, in a human maximization test, no reactions indicative of sensitization were observed to read-across material benzyl acetate (Greif, 1967). In Confirmation of No Induction in Humans tests (CNIHs) up to 8% (9448 μg/cm^2) of read-across material benzyl acetate in 3:1 ethanol:diethylphthalate (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 the weight of evidence (WoE) from structural analysis, animal and human studies, and read-across to benzyl acetate, benzyl valerate 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: 05/20/21.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, benzyl valerate would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for benzyl valerate in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, benzyl valerate does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) 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 photoirritating 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

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

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 study conducted in rats with nose-only inhalation exposure, a NOAEC of 614 mg/m^3 was reported for benzyl acetate (RIFM, 2013a). 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)/(1 m^3/1000 L) = 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 0.000097 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015 and Safford et al., 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 0.00015 mg/kg lung weight/day resulting in a MOE of 15666667 (i.e., [2350 mg/kg lung weight/day]/[0.00015 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 0.000097 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey=9100R7VE.PDF.

**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); The Union of German Candle Manufacturers (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, 2014a; 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 valerate was performed following the RIFM Environmental Framework (Salvito, 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 VoU 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 valerate 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 valerate 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, 2017a). 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).

11.2.1.1. Risk assessment. Based on the current VoU (2015), benzyl valerate does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.3. Ecotoxicity. No data available.

11.2.1.4. Other available data. Benzyl valerate has been pre-registered for REACH with no additional data at this time.

11.2.1.5. 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.

	(Fish) (mg/L)	(*Daphnia*) (mg/L)	(Algae) (mg/L)			
RIFM Framework Screening-level **(Tier 1)**	<u>11.62</u>			1000000	0.01162	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.55	3.55
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	No volume reported
Risk Characterization: PEC/PNEC	**<1**	**NA**

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

The RIFM PNEC is 0.01162 μg/L. The revised PEC/PNECs for EU and NA (No VoU) are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

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

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
  - **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
  - **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 ChemView:** https://chemview.epa.gov/chemview/
  - **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/17/22.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113455.

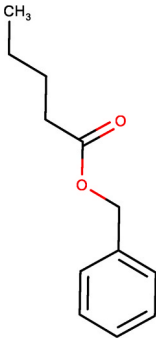
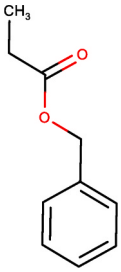
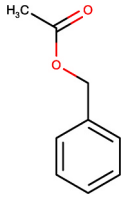
Appendix

Read-across justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were 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 material 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Benzyl valerate	Benzyl propionate	Benzyl acetate
CAS No.	10,361-39-4	122-63-4	140-11-4
Structure			
Similarity (Tanimoto Score)		0.83	0.71
SMILES	CCCCC(=O)OCc1ccccc1	CCC(=O)OCc1ccccc1	CC(=O)OCc1ccccc1
Endpoint		Genotoxicity	• Skin sensitization • Repeated dose toxicity • Reproductive toxicity • Local respiratory toxicity
Molecular Formula	$C_{12}H_{16}O_2$	$C_{10}H_{12}O_2$	$C_9H_{10}O_2$
Molecular Weight (g/mol)	192.258	164.204	150.177
Melting Point (°C, EPI Suite)	32.02	10.60	−51.30
Boiling Point (°C, EPI Suite)	269.08	220.00	213.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.15E+00	1.75E+01	2.36E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.42E+01	4.16E+02	3.10E+03
Log K_{OW}	3.55	2.57	1.96
J_{max} (μg/cm^2/h, SAM)	3.19	15.45	64.04
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.35E+00	1.90E+00	1.14E+00
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	
Carcinogenicity (ISS)	No alert found	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	
Oncologic Classification	Not classified	Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Pethidine (Hepatotoxicity) Alert|Toluene (Renal toxicity) Alert		Menadione (Hepatotoxicity) Alert|Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH_2 group		Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		Toxicant (moderate reliability)
Skin Sensitization			
Protein Binding (OASIS v1.1)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters
Protein Binding (OECD)	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals		SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ 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 (OASIS v1.1)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Acyl Transfer agent identified.		Alert for Acyl Transfer agent identified.
Local Respiratory Toxicity			
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	No alert found		No alert found
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

Benzyl butyrate (CAS # 10,361-39-4) lacks toxicity data for the genotoxicity, repeated dose toxicity, reproductive toxicity, skin sensitization, and local respiratory toxicity endpoints. Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, benzyl propionate (CAS # 122-63-4) and benzyl acetate (CAS # 140-11-4) were identified as read-across analogs for their respective toxicity endpoints.

Conclusions

- Benzyl propionate (CAS # 122-63-4) was used as a read-across analog for the target material benzyl valerate (CAS # 10,361-39-4) for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of benzylic esters.
  - o The key difference between the target material and the read-across analog is that the target material is a valerate ester while the read-across analog is a propionate ester. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have an alert for Michael addition and quinone formation. This is due to the presence of a benzene ring in the structure, which can undergo epoxidation and quinone formation. The data for the read-across analog confirms that the analog does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and data on the read-across analog, the alerts are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Benzyl acetate (CAS # 140-11-4) was used as a read-across analog for the target material benzyl valerate (CAS # 10,361-39-4) for the skin sensitization, repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints.
  - o The target material and the read-across analog belong to a class of benzylic esters.
  - o The key difference between the target material and the read-across analog is that the target material is a valerate ester while the read-across analog is an acetate ester. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have an alert SN2 reaction. This is due to the presence of a benzene ring in the structure, which can undergo epoxidation and quinone formation. The data for the read-across analog confirms that the analog does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and data on the read-across analog, the alerts are superseded by the data.
  - o The target material and the read-across analog have menadione hepatotoxicity and toluene renal toxicity alert. They also have been predicted by the CAESAR model to be toxicants. These alerts are due to benzylic alcohol and the reactivity of aromatic rings. The data on the read-across analog confirms that it does not pose a concern for any of these endpoints at current levels of use. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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