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Short review

RIFM fragrance ingredient safety assessment, benzyl formate, CAS Registry Number 104-57-4

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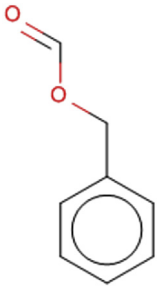
Version: 092717. This version replaces any previous versions.
Name: Benzyl formate
CAS Registry Number: 104-57-4



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

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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
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
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 formate) 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 phenethyl formate (CAS # 104-62-1) show that benzyl formate is not genotoxic. Data from the read across analog benzyl acetate (CAS # 140-11-4) show that benzyl formate does not have skin sensitization potential and provided a MOE > 100 for the repeated dose, developmental and reproductive, and local respiratory toxicity endpoints. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, benzyl formate 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. (RIFM, 2015b; RIFM, 2015a)
Repeated Dose Toxicity: NOAEL = 260 mg/kg/day. (National Toxicology Program, 1993)
Developmental Toxicity: NOAEL = 100 mg/kg/day; **Reproductive Toxicity:** NOAEL = 460 mg/kg/day. (Ishiguro et al., 1993; National Toxicology Program, 1993)
Skin Sensitization: Not a sensitization concern. (RIFM, 1987; RIFM, 1988a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: NOAEC = 61.4 mg/m^3 (RIFM, 2013)

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 71% (EEC Method C.4-E) (RIFM, 2000)
Bioaccumulation: Screening Level: 4.77 L/kg (US EPA, 2012a)
Ecotoxicity: Screening Level: LC50: 470 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: LC50: 470 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.470 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 formate
2. **CAS Registry Number**: 104-57-4
3. Synonyms: Benzyl methanoate; Formic acid, phenylmethyl ester; ｱﾙｶﾝ酸(C = 1 ~ 6)ﾍﾞﾝｼﾞﾙ; Benzylformiat; Benzyl formate
4. **Molecular Formula**: $C_8H_8O_2$
5. **Molecular Weight**: 136.15
6. **RIFM Number**: 228

2. Physical data

1. **Boiling Point:** 205 °C [FMA Database], 197.78 °C [US EPA, 2012a]
2. **Flash Point:** 82 °C [GHS Database], 180 °F; CC [FMA Database]
3. **Log K_{OW}:** 1.53 [US EPA, 2012a]
4. **Melting Point**: −3.15 °C [US EPA, 2012a]
5. **Water Solubility:** 4257 mg/L [US EPA, 2012a]
6. **Specific Gravity**: 1.080 [FMA Database]
7. **Vapor Pressure:** 0.209 mm Hg @ 20 °C [US EPA, 2012a], 0.2 mm Hg 20 °C [FMA Database], 0.31 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Givaudan Index (1961) Colorless liquid with a powerful, fruity-green, herbaceous-earthy, yet somewhat floral odor. Has a very sweet taste, more fruity than floral.

3. Exposure

1. **Volume of Use (Worldwide Band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.0050% (RIFM, 2016e)
3. **Inhalation Exposure*:** 0.000027 mg/kg/day or 0.0020 mg/day (RIFM, 2016e)
4. **Total Systemic Exposure**:** 0.00052 mg/kg/day (RIFM, 2016e)

*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**: Assumed 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:** Phenethyl formate (CAS # 104-62-1)
   b. **Repeated Dose Toxicity:** Benzyl acetate (CAS # 140-11-4)
   c. **Developmental and Reproductive Toxicity**: Benzyl acetate (CAS # 140-11-4)
   d. **Skin Sensitization:** Benzyl acetate (CAS # 140-11-4)
   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 formate is reported to occur in the following foods* and in some natural complex substances (NCS):

Cherry
Coffee
Crowberry (*Empetrum nigrum coll.*)
Mushroom
Ocimum species
Passion fruit (*Passiflora* species)
Plum (*Prunus* species)
Tea
Vaccinium species
Vanilla

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Available, accessed 8/31/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, benzyl formate does not present a concern for genotoxic potential.

10.1.1.1. Risk assessment. The mutagenic activity of benzyl formate 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 and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with benzyl formate in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2015b). Under the conditions of the study, benzyl formate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of benzyl formate; however, read across can be made to phenethyl formate (CAS # 104-62-1; see Section 5). The clastogenic activity of phenethyl formate was assessed 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 phenethyl

formate in DMSO at concentrations ranging from 100 to 1500 μg/plate with and without metabolic activation. The percentage of cells with micronucleated binucleated cells in the test substance-treated groups was not statistically significantly increased relative to vehicle control at any dose level (RIFM, 2015a). Based on the findings of the study phenylethyl formate was concluded to be negative for the induction of micronuclei in the *in vitro* mammalian cell micronucleus test using human peripheral blood lymphocytes and this can be extended to benzyl formate.

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

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/14/15.

10.1.2. Repeated dose toxicity

The margin of exposure for benzyl formate 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 formate. 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 the males and 0, 240, 480, 930, 1870 or 4500 mg/kg/day for the females) for 13 weeks. Mortality was reported among the 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 the 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 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 high dose animals. There were no alterations reported among the 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 (National Toxicology Program, 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. Body weight gains and final body weights (8–31% lower among the males and 12–33% lower among the females) among the treated animals were significantly lower than the control. Food consumption among the males of the 3100 ppm males and all treated females was lower than the control. Alterations in organ weights were reported among the 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 the females of the 12500 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 one high dose male characterized by necrosis of the hepatocytes of moderate severity randomly distributed throughout the hepatic lobules. No other test material related alterations were reported among the animals of the 6250 ppm or lower dose groups. Due to a 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 (National Toxicology Program, 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 slightly lower mean body weights than the controls. Food consumption was slightly reduced in the high dose males; there were no differences in food consumption in the females. Food consumption among the high dose males was lower than 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 (National Toxicology Program, 1993).

In another 2-year chronic toxicity 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 mg/kg/day 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 the treated and control group mice. In the 2-year NTP study 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). 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 (National Toxicology Program, 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 was considered which was derived from the 2-year chronic study conducted on rats.

Therefore, the benzyl formate 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 formate, 260/0.00052 or 500000.

In addition, the total systemic exposure to benzyl formate (0.52 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, 1986b.

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

10.1.3. Developmental and reproductive toxicity

The margin of exposure for benzyl formate 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 toxicity data on benzyl formate. 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, 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 produce teratogenic effects. Thus, the developmental toxicity NOAEL was considered to be 100 mg/kg/day. Therefore, the benzyl formate 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 formate, 100/0.00052 or 192308.

There are no reproductive toxicity data on benzyl formate. Read across material, benzyl acetate (CAS # 140-11-4; see Section 5) has sufficient reproductive 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. Detailed histopathological evaluations included the male (preputial gland, 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 smear were evaluated among the 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 the treated animals. Thus, the NOAEL for the reproductive toxicity was considered to be 6250 ppm 460 or 480 mg/kg/day for the males and females, respectively (National Toxicology Program, 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 included 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 smear were evaluated among the treated rats. 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 the treated animals. A significant dose-related decrease in body weight and significant lengthening of the estrous cycle was reported among the female mice. The lengthening of the estrous cycle was reported to be related to the significant decrease in body weights (~30%) and food consumption, hence not considered to be an adverse effect. Thus, the NOAEL was considered to be 50000 ppm or 7900 or 9400 mg/kg/day for the males and females, respectively (National Toxicology Program, 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 formate 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 formate, 460/0.00052 or 884615.

In addition, the total systemic exposure to benzyl formate (0.52 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, 1986b.

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

10.1.4. Skin sensitization

Based on the available data and read across to benzyl acetate (CAS # 140-11-4), benzyl formate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data and read across to benzyl acetate (CAS # 140-11-4; see Section 5), benzyl formate does not present a concern for skin sensitization. The chemical structure of these materials indicates that they could possibly react with proteins, although little or no reaction would likely occur under physiological conditions (Roberts et al., 2007; Toxtree 2.6.13). However, benzyl formate was found to be minimally reactive in the *in vitro* Direct Peptide Reactivity Assay (DPRA) (RIFM, 2016c). Similarly, in the human cell line activation test (hCLAT), benzyl formate was found to be negative up to 578.7 μg/mL (RIFM, 2016d). In open epicutaneous tests in guinea pigs, no reactions indicative of sensitization were observed with benzyl formate (Klecak, 1979 and Klecak, 1985). Moreover, in several guinea pig test methods, no reactions indicative of sensitization were observed with read across analog benzyl acetate (RIFM, 1985b; RIFM, 1986a; RIFM, 1985a; RIFM, 1985c). In a human maximization test, no skin sensitization reactions were reported with benzyl formate and benzyl acetate (RIFM, 1971; Greif, 1967). Additionally, in the human repeat insult patch test with up to 8% (9448 μg/cm^2) benzyl acetate in ethanol:diethylphthalate (75:25), no reactions indicative of skin sensitization were observed (RIFM, 1987; RIFM, 1988a). Based on weight of evidence from structural analysis, *in chemico*, *in vitro* test methods, animal and human studies as well as read across to benzyl acetate, benzyl formate does not present a concern for skin sensitization.

Additional References: Sharp, 1978; RIFM, 1962; Klecak, 1979, 1985; Ishihara et al., 1986; Greif, 1967; RIFM, 1988b; RIFM, 1988c; RIFM, 1988d; RIFM, 1975e; RIFM, 1975d; RIFM, 1975c; RIFM, 1975b; RIFM, 1975a; RIFM, 1961.

Literature Search and Risk Assessment Completed on: 2/24/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, benzyl formate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for benzyl formate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L · mol^{-1} · cm^{-1} (Henry et al., 2009). Based on lack of absorbance, benzyl formate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

10.1.6. Local respiratory toxicity

There are no inhalation data available on benzyl formate; 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 (2013).

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, 2013). 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 0.0019 mg/day—this value was derived from the concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015; Safford et al., 2015, 2017; Comiskey et al., 2017). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.0029 mg/kg lung weight/day resulting in a MOE of 810345 (i.e., [2350 mg/kg lung weight/day]/[0.0029 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 0.0019 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, 2003a, 2003b; RIFM, 2003a; Rogers et al., 2003; RIFM, 2003b; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Isola et al., 2004; 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 formate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (US EPA, 2012b; providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, Benzyl formate 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 formate 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). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

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

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 2000: The biodegradability of the test material was determined using the Closed Bottle Test according to the EEC Method C.4-E. 3.3 mg/L test material was suspended in a mineral medium, inoculated with a mixed population of aquatic microorganisms (activated sludge) and incubated for 28 days. Biodegradation of 71% was observed.

10.2.3.2. Ecotoxicity. RIFM, 2000: A *Daphnia magna* acute toxicity study was conducted according to the Council Directive 92/69/EEC C.2 in a static system. The 48-h EC0 was reported to be = > / = 102.2 mg/L (arithmetic mean of analytical values).

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

11. Risk assessment refinement

Since benzyl formate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	<u>470 mg/L</u>			1,000,000	0.470 µg/L	

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.53	1.53
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 0.470 µg/L. The revised PEC/PNECs for EU and NA: Not Applicable; 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: 1/13/15.

12. 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.2018.01.007.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2018.01.007.

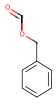
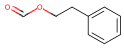
Appendix

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 SuiteTM v4.11 (US EPA, 2012a).
- Jmax 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 formate	Phenethyl formate	Benzyl acetate
CAS No.	104-57-4	104-62-1	140-11-4
Structure			
Similarity (Tanimoto score)		0.94	0.95

Read across endpoint		• Genotoxicity	• Respiratory • Repeated dose • Developmental and reproductive • Skin sensitization
Molecular Formula	$C_8H_8O_2$	$C_9H_{10}O_2$	$C_9H_{10}O_2$
Molecular Weight	136.15	150.18	150.18
Melting Point (°C, EPISUITE)	−3.15	8.20	−0.50
Boiling Point (°C, EPISUITE)	197.78	217.34	215.57
Vapor Pressure (Pa @ 25 °C, EPISUITE)	41.4	20	25
Log Kow (KOWWIN v1.68 in EPISUITE)	1.79[1]	2.0	1.96
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	2890[2]	1413	3100
J_{max} (mg/cm^2/h, SAM)	64.707	42.164	64.032
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.94E-005	2.57E-005	1.42E-005
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition	• Michael addition	
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	
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	• Aldehyde type compounds	• Aldehyde type compounds	
Repeated dose toxicity			
Repeated Dose (HESS)	• Not categorized		• Not categorized
Reproductive and developmental to*xicity*			
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	• No alert found		• SN2 reaction
Protein binding by OECD	• No alert found		• SN2 reaction
Protein binding potency	• Not possible to classify		• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.4	• No alert found		• SN2 reaction
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (low 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	See supplemental data 3 • **Observed Mammalian metabolism:** See supplemental data 4 • **Observed Rat *In vivo* metabolism:** See supplemental data 5

NA[a] Major metabolites or analog of major metabolites of the target substance.
[1]RIFM, 2016a.
[2]RIFM, 2016b.
[3]Chidgey et al., 1987.
[4]McMahon et al., 1989.

Summary:

There are insufficient toxicity data on the target material benzyl formate (CAS # 104-57-4). 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, analogs phenethyl formate (CAS # 104-62-1) and benzyl acetate (CAS # 140-11-4) were identified as read across materials with data for their respective toxicological endpoints.

Conclusion/Rationale:

- For the target material benzyl formate (CAS # 104-57-4), phenethyl formate (CAS # 104-62-1) was used as a read across analog for the

genotoxicity endpoint and benzyl acetate (CAS # 140-11-4) was used as a read across analog for the skin sensitization, local respiratory, reproductive and developmental toxicity, and repeated dose toxicity endpoints.

- The target substance and the read across analogs are structurally similar and belong to the structural class of esters with primary aryl alcohol.
- The target substance and the read across analogs share a primary aryl alcohol ester structure.
- The key difference between the target substance and the read across analogs is in the aliphatic fragments on the acid and alcohol portion. The target is an ester of formic acid and benzyl alcohol. The read across analog, phenethyl formate, is an ester of formic acid and phenethyl alcohol, while the read across analog, benzyl acetate, is an ester of acetic acid and benzyl alcohol. This structural difference between the target substance and the read across analogs does not affect consideration of the toxicological endpoint.
- Similarity between the target substance and the read across analogs is indicated by the a Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoints.
- The physical-chemical properties of the target substance and the read across analogs are sufficiently similar to enable comparison of their toxicological properties.
- According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicological endpoints are consistent between the target substance and the read across analog.
- The target substance and the read across analog phenethyl formate have been classified as aldehyde type compounds by OECD QSAR Toolbox. This is mainly due to formation of a primary alcohol via metabolic hydrolysis followed by metabolic oxidation to aldehydes. Other genotoxicity alerts for both of the substances are negative. Data described in the genotoxicity section above shows that the read across analog does not pose a concern for the genotoxicity endpoint. Therefore, the alert is superseded by the availability of data.
- According to the CAESAR model for developmental and reproductive toxicity, the read across analog, benzyl acetate, is predicted to be a toxicant while no such alert is given for the target substance. According to this prediction, the read across analog is expected to be more reactive compared to the target substance. Data described in the developmental and reproductive toxicity section show that the margin of exposure for the read across analog, benzyl acetate, is adequate at the current level of use. The alert is superseded by the availability of data.
- Protein binding alert for skin sensitization by OASIS model predicts that the read across analog, benzyl acetate, is susceptible to SN2 reaction. The target does not have this alert by OASIS model. This alert predicts the read across analog to be more reactive compared to the target substance for the skin sensitization endpoint. Also, the CAESAR model predicts the target and the read across analog benzyl acetate to be sensitizers. Other protein binding alerts for both of the substances are negative. The data described in the skin sensitization section above show that the read across analog does not pose a concern for the skin sensitization endpoint. Therefore, this alert will be superseded by the availability of data.
- The target substance and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

- **Metabolism**

Metabolism of the target substance was not considered for the risk assessment and therefore metabolism data were not reviewed, except where it may pertain in specific endpoint sections above. Metabolism of the target material benzyl formate (CAS # 104-57-4) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). The target material is predicted to metabolize to benzyl alcohol (CAS # 100-51-6) and formic acid (CAS # 64-18-6) in the first step with 0.95 pre-calculated probability. Benzyl alcohol was out of domain for the *in vivo* and *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgement, the model's domain exclusion was overridden and a justification is provided.

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