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Short review

RIFM fragrance ingredient safety assessment, Benzyl acetate, CAS Registry Number 140-11-4

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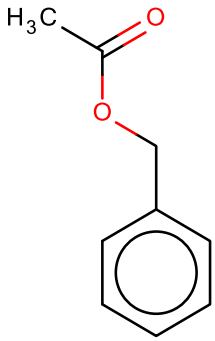

Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th **percentile** – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th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

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on RIFM's Criteria Document (Api et al., 2015) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria such as, acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.
Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential as well as environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 14.5 mg/kg/day, based on a dietary 2-year chronic toxicity study conducted in rats, that resulted in a MOE of 145 considering 78.7% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

(*continued*)

Human health safety assessment	
Genotoxicity: Not genotoxic.	(Shelby et al., 1993; Tennant et al., 1987)
Repeated dose toxicity: NOAEL = 14.5 mg/kg/day	(NTP, 1993)
Developmental and reproductive toxicity: NOAEL = 100 mg/kg/day	(Ishiguro et al., 1993)
Skin sensitization: Not sensitizing	(RIFM, 1985b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM DB; RIFM, 1983)
Local respiratory toxicity: NOAEC = 61.4 mg/m^3 or 10 ppm	(RIFM, 2013)
Environmental safety assessment	
Hazard assessment:	
Persistence: Critical Measured Value: 99.7% (OECD 301B)	(RIFM, 1994a)
Bioaccumulation: Screening Level: 9.12 L/Kg	(EPISUITE ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 28 day Fish chronic: 0.92 mg/l	(Holcombe et al., 1995)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(Salvito et al., 2002)
Critical ecotoxicity endpoint: 28 day Fish chronic: 0.92 mg/l	
RIFM PNEC is: 9.2 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe <1	

1. Identification

1. **Chemical name:** Benzyl acetate
2. **CAS registry number:** 140-11-4
3. **Synonyms:** Benzyl acetate, Acetic acid, phenylmethyl ester, Benteine, Benzyl ethanoate, Methyl α-toluate, Methyl phenylethanoate, Methyl benzeneacetate, Acetic acid, benzyl ester, Phenylmethyl acetate, ｱﾙｶﾝ酸(C = 1 ~ 6)ﾍﾞﾝｼﾞﾙ, ｱﾙｷﾙ(C = 1 ~ 5)ｶﾙﾎﾞﾝ酸ﾌｪﾆﾙｱﾙｷﾙ(C = 1 ~ 6)
4. **Molecular formula:** $C_9H_{10}O_2$
5. **Molecular weight:** 150.18
6. **RIFM number:** 106

2. Physical data

1. **Boiling point:** 216 °C [FMA database], (calculated) 215.57 °C [EPI Suite]
2. **Flash point:** 195 °F; CC [FMA database]
3. **Log K_{OW}:** 2.0 at 35 °C [Givaudan, 2004q], 2.08 [EPI Suite]
4. **Melting point**: −0.5 °C [EPI Suite]
5. **Water solubility:** 1454 mg/L (mean) at 20 ± 0.5 °C [RIFM, 1992], (calculated) 1605 mg/L [EPI Suite]
6. **Specific gravity:** 1.06 g/ml [RIFM, 1994a], 1.054–1.058 [FMA], 1.052–1.056 [FMA database]
7. **Vapor pressure:** 0.125 mm Hg @ 20 °C [EPI Suite 4.0], 0.1 mm Hg 20 °C [FMA], 0.187 mm Hg @ 25 °C [EPI Suite]
8. **UV spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1}).
9. **Appearance/Organoleptic:** Colorless to very pale yellow liquid having a characteristic floral odor.

III. EXPOSURE	
1. Volume of use (worldwide band): >1000 metric tons per year	[IFRA, 2011]
2. Average maximum concentration in hydroalcoholics: 4.17%	[IFRA, 2008]
3. 97.5 th **percentile:** 4.51%	[IFRA, 2008]
4. Dermal exposure*: 0.1150 mg/kg/day	[IFRA, 2008]
5. Oral exposure: Not available	
6. Inhalation exposures:** 0.0069 mg/kg/day	[IFRA, 2008]
7. Total systemic exposure (dermal + inhalation): (0.1150 mg/kg/day × 78.7% absorption) + 0.0069 mg/kg/day = 0.10 mg/kg/day	

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

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

3. Derivation of systemic absorption

1. **Dermal:** 78.7%
   Bronaugh et al., 1990: The skin absorption of [7−^{14}C] benzyl acetate was measured in 4 female rhesus monkeys. The test material in acetone was applied at a concentration of 4 μg/cm^2 to a 1 cm^2 area of abdominal skin for 24 h. Urine was collected for an additional 4 days. The extent of dermal absorption was estimated from the amount of ^{14}C-equivalents excreted in the urine over the 5 day collection period. When the application site was occluded with either plastic wrap or a glass chamber, the absorption of benzyl acetate was 17.3 ± 2.7% and 78.7 ± 7.5%, respectively. When the site was not occluded, the absorption was 34.6 ± 9.4%. For conservative purposes 78.7% absorption is considered.
2. **Oral:** Data not available − not considered.
3. **Inhalation:** Assumed 100%

4. **Total:** Dermal (78.7%) + Inhalation (assume 100%) absorbed = (0.1150 mg/kg/day x 78.7%) + 0.0099 mg/kg/day = 0.10 mg/kg/day

4. Computational toxicology evaluation

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

Expert Judgment	Toxtree 2.6	OECD QSAR Toolbox 3.1
I	I	I

2. **Analogues selected**:
   a. **Genotoxicity:** None
   b. **Repeated dose toxicity:** None
   c. **Developmental and reproductive toxicity:** None
   d. **Skin sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local respiratory toxicity:** None
   g. **Environmental toxicity:** None
3. **Read-across justification:** None

5. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

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

Apple brandy (Calvados)	Litchi wine
Apple fresh (Malus species)	Manigera species
Apple processed (Malus species)	Mate (Ilex paraguayensis)
Arctic bramble (Rubus arcticus L.)	Matsutake (Tricholoma matsutake)
Avocado (Persea americana Mill.)	Melon
Beli, bael (Aegle marmelos Correa)	Mountain papaya (C. candamarcensis, C. pubescens)
Bilberry wine	Mushroom
Brassica campestris	Mustard (Brassica species)
Camomile	Naranjilla fruit (Solanum quitoense Lam.)
Cherimoya (Annona cherimolia Mill.)	Ocimum species
Cherry	Olive (Olea europaea)
Cherry brandy	Passion fruit (passiflora species)
Chinese quince (Pseudocydonia sinensis Schneid)	Peach (Prunus persica L.)
Citrus fruits	Plum (Prunus species)
Cloudberry (Rubus chamaemorus L.)	Plum brandy
Cloves (Eugenia caryophyllata Thunberg)	Quince, marmelo (Cydonia oblonga Mill.)
Cocoa category	Rambutan (Nephelium lappaceum L.)
Dwarf quince (Chaenomeles japonica)	Raspberry, blackberry and boysenberry
Filbert, hazelnut (Corylus avellano)	Rice (Oryza sativa L.)
Grape (Vitis species)	Rutabaga, swede (Brass. napus var. napobrass. L.)
Grape brandy	Strawberry (Fragaria species)
Guava and feyoa	Tapereba, caja fruit (Spondias lutea L.)
Hog plum (Spondias mombins L.)	Tea
Honey	Vinegar
Tomato (Lycopersicon esculentum Mill.)	Whisky
Vaccinium Species	Wine
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.

7. IFRA standard

None.

8. REACH dossier

Available, accessed on 09/12/13: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d81dbc9-cd1b-5141-e044-00144f67d249/DISS-9d81dbc9-cd1b-5141-e044-00144f67d249_DISS-9d81dbc9-cd1b-5141-e044-00144f67d249.html.

9. Summary

9.1. Human health endpoint summaries

9.1.1. Genotoxicity

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

9.1.2. Risk assessment

The mutagenic potential of benzyl acetate was assessed in an Ames assay performed similar/equivalent to OECD TG 471 using the standard plate incorporation method. Four *Salmonella typhimurium* strains were tested at a maximum dose of 10,000 μg/plate in the presence and absence of metabolic activation (S9 mix). (Tennant et al., 1987). The study concluded that benzyl acetate is not mutagenic under the conditions of this test.

The clastogenic potential of benzyl acetate was assessed in an *in vivo* micronucleus test conducted by the NTP. No significant increase in the frequency of micronucleated erythrocytes was observed and the test article was considered not clastogenic (NTP, 1993).

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

9.1.3. Additional references

NTP, 1993; Florin et al., 1980; Mortelmans et al., 1986; Yoo, 1986; Caspary et al., 1988; Galloway et al., 1987; Rudd et al., 1983; Rogan et al., 1986; McGregor et al., 1988; Schunk et al., 1986; Longnecker et al., 1990; Elmore and Fitzgerald, 1990; Mirsalis et al., 1989, 1983; Foureman et al., 1994; Steinmetz and Mirsalis, 1984; Yoshikawa, 1996; Matsuoka et al., 1996; Miyagawa et al., 1995; Mitchell and Caspary, 1987; Zimmermann et al., 1989; Honma et al., 1999; Kevekordes et al., 1999; Rossman et al., 1991; Witt et al., 2000; Sasaki et al., 2000; Yoo, 1985; Kevekordes et al., 2001; Sekihashi et al., 2002; Yasunaga et al., 2004; Oda et al., 1978; Scott et al., 2007; Demir et al., 2010.

9.1.4. Literature search and risk assessment completed on

09/16/13.

9.1.5. Repeated dose toxicity

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

9.1.6. Risk assessment

There are numerous oral repeated dose toxicity studies conducted with benzyl acetate in rats and mice. A dietary 2-year chronic toxicity study conducted in rats determined a LOAEL for repeated dose toxicity of 3000 ppm, or 145 mg/kg/day for female rats, based on decreased body weights (NTP, 1993). The NOAEL was derived by dividing the LOAEL by a safety factor of 10, which is equal to 14.5 mg/kg/day. **Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 14.5/0.10 or 145**.

9.1.7. Additional references

McGinty et al., 2012; Belsito et al., 2012; RIFM, 2013; RIFM, 1986b; RIFM, 1957; Abdo and Wenk, 1995, Abdo et al., 1998; Longnecker et al., 1986; Longnecker et al., 1990; Young, 1989; Abdo et al., 1985; Caldwell et al., 1987; Snapper et al., 1925; Hotchkiss et al., 1992a; Nasseri-Sina et al., 1992; Chidgey et al., 1986; Grundschober, 1977; Miyashita and Robinson, 1980; Chidgey and Caldwell, 1986, Chidgey et al., 1987; McMahon et al., 1989a; Augustinsson and Ekedahl, 1962; Clapp and Young, 1970; McMahon et al., 1989b; Schunk et al., 1986; RIFM, 1989b; Hotchkiss 1998, Hotchkiss et al., 1992b, 1992c; Caldwell et al., 1987; Meyer, 1965; Garnett et al., 1994; Jimbo, 1983; Hotchkiss et al., 1988, 1990a, 1990b, 1989; Hotchkiss et al., 1990a; Hotchkiss et al., 1990b; RIFM, 1989a; Hotchkiss et al., 1992d;

9.1.8. Literature search and risk assessment completed on

09/16/13.

9.1.9. Developmental and reproductive toxicity

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

9.1.10. Risk assessment

The developmental toxicity data on benzyl acetate are sufficient for the developmental toxicity endpoint. A gavage developmental toxicity study conducted in rats determined the NOAEL for developmental toxicity to be 100 mg/kg/day, based on minor fetal internal anomalies and fetal weights (Ishiguro et al., 1993). **Therefore, the MOE for developmental toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.10 or 1000**.

There are no reproductive toxicity data on benzyl acetate. The gavage developmental toxicity study conducted in rats determined the NOAEL for maternal toxicity to be 500 mg/kg/day, based on maternal body weight gain (Ishiguro et al., 1993). In a 13-week dietary subchronic toxicity studies in rats and mice, sperm morphology and vaginal cytology examinations were evaluated (Morrissey et al., 1988). There were no effects on sperm parameters in mice or rats up to the high dosage of 7900 or 3900 mg/kg/day, respectively. There were no effects on estrous cycling in female rats up to the high dosage of 4500 mg/kg/day. Lengthening of the estrous cycle occurred in high-dose female mice (9400 mg/kg/day), which the authors concluded was related to decreases in body weight. These data indicate no specific concern for reproductive toxicity. **Therefore, the MOE for reproductive toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.10 or 5000.**

RIFM's Expert Panel* and the adjunct Reproduction Advisory Group* reviewed the Ishiguro (Ishiguro et al., 1993) results and concluded that the minor fetal anomalies observed at the highest dose level were most likely a developmental delay. An increased fetal body weight may indicate an adverse effect. For example, chemicals which induce maternal diabetes mellitus may increase fetal weight. Early embryocidal effects leading to a reduced litter size may secondarily increase fetal weight. The Panel members and the Reproduction Advisory Group concluded that the increased fetal body weight observed in the 100 and 10 mg/kg/day groups was biologically insignificant and that no additional reproductive or developmental toxicity studies are needed. They concluded that the maternal NOAEL was 500 mg/kg/day based on weight gain and the fetal NOAEL is 100 mg/kg/day based on weight and internal organ malformations.

*RIFM's Expert Panel and adjunct Reproduction Advisory Group are composed of scientific and technical experts in their respective fields. These groups provide advice and guidance.

9.1.11. Additional references

McGinty et al., 2012; Belsito et al., 2012; RIFM, 2013; RIFM, 1986b; RIFM, 1957; Abdo and Wenk, 1995, Abdo et al., 1998; Longnecker et al., 1986; Longnecker et al., 1990; Young, 1989; Abdo et al., 1985; Caldwell et al., 1987; Snapper et al., 1925; Hotchkiss et al., 1992a; Nasseri-Sina et al., 1992; Chidgey et al., 1986; Grundschober, 1977; Miyashita and Robinson, 1980; Chidgey and Caldwell, 1986, Chidgey et al., 1987; McMahon et al., 1989a; Augustinsson and Ekedahl, 1962; Clapp and Young, 1970; McMahon et al., 1989b; Schunk et al., 1986; RIFM, 1989b; Hotchkiss 1998, Hotchkiss et al., 1992b, 1992c; Caldwell et al., 1987; Meyer, 1965; Garnett et al., 1994; Jimbo, 1983; Hotchkiss et al., 1988, 1990a, 1990b, 1989; Hotchkiss et al., 1990a; Hotchkiss et al., 1990b; RIFM, 1989a; Hotchkiss et al., 1992d.

9.1.12. Literature search and risk assessment completed on

09/16/13.

9.1.13. Skin sensitization

Based on the available data, benzyl acetate does not present a concern for skin sensitization.

9.1.14. Risk assessment

While the chemical structure of this material indicates that it would be expected to react with skin proteins, the reactivity is expected to be low (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In guinea pig test methods no reactions indicative of sensitization were observed (Bronaugh et al., 1982; RIFM, 1985b; RIFM, 1986a; RIFM, 1985a; Klecak, 1985). Additionally, no reactions indicative of skin sensitization were observed in both the human repeated insult patch test and the human maximization test (RIFM, 1987; RIFM, 1975e; RIFM, 1975d; RIFM, 1975c; RIFM, 1975b; RIFM, 1975a; RIFM, 1988a; RIFM, 1988b; NTP, 1993; RIFM, 1988c; RIFM, 1988d; RIFM, 1961). Based on the available data, benzyl acetate does not present a concern for skin sensitization.

9.1.15. Additional references

None.

9.1.16. Literature search and risk assessment completed on

05/05/14.

9.1.17. Phototoxicity/photoallergenicity

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

9.1.18. Risk assessment

UV/Vis absorption spectra (OECD test guideline 101) for benzyl

acetate demonstrate no absorbance between 290 and 700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). In a Guinea pig phototoxicity study no reactions indicative of phototoxic responses were observed (RIFM, 1983). Based on lack of absorbance in the critical range and existing data, benzyl acetate does not present a concern for phototoxicity or photoallergenicity.

9.1.19. Additional references

None.

9.1.20. Literature search and risk assessment completed on

05/05/14.

9.1.21. Local respiratory toxicity

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

9.1.22. 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 nose-only inhalation exposure acute 2 week study done in rats, a NOAEC of 100 ppm (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 (10 ppm; the mid dose given) was considered.

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

- (61.4 mg/m^3)/(1m^3/1000L) = 0.0614 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague–Dawley rat X duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- (0.0614 mg/L) (61.2 L/d) = 3.76 mg/d
- (3.76 mg/d)/(0.0016 kg lung weight of rat*) = 2348 mg/kg lw/day

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 4.51%. If the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.42 mg/day as calculated based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual using RIFM's 2-Box/MPPD in-silico models. To compare this estimated exposure with the benzyl acetate 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, 0.65 mg/kg lung weight/day resulting in an MOE of 3612 (i.e., [2348 mg/kg lw/day]/[0.65 mg/kg lung weight/day]).

Since the MOE is greater than 100 the material exposure, by inhalation, at 4.51% in a combination of the products noted above, is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy", subsection, "Comparative Airway Anatomy."

9.1.23. Additional references

RIFM, 1977; RIFM, 1997b; Silver, 1992; RIFM, 1997a; Isola et al., 2003a; Rogers et al., 2003; RIFM, 2003b; RIFM, 2003a; Isola et al., 2003b; Isola et al., 2004a; Smith et al., 2004; RIFM, 2004; Isola et al., 2004b; Rogers et al., 2005; Randazzo et al., 2014; Vethanayagam et al., 2013.

9.1.24. Literature search and risk assessment completed on

09/16/13.

9.2. Environmental endpoint summary

9.2.1. Screening-level assessment

A screening level risk assessment of benzyl acetate was performed following the RIFM Environmental Framework. The RIFM Environmental Framework (Salvito et al., 2002) 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 (PEC/PNEC)). In Tier 1 a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2 the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3 measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Following the RIFM Environmental Framework, benzyl acetate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1). A screening-level hazard assessment using EPISUITE ver 4.1 did not identify benzyl acetate as being either persistent or bioaccumulative based on its structure and physical–chemical properties.

9.2.2. Risk assessment

Based on current VoU from 2011, benzyl acetate presents a risk to the aquatic compartment.

9.2.3. Key studies

9.2.3.1. Biodegradation. A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test according to the OECD 301B method. The biodegradation rate was 99.7% at day 28 (RIFM, 1994a).

9.2.3.2. Ecotoxicity. A *Daphnia magna* immobilization study following OECD Test Guideline 202 was reported. The 48 h EC50 was 37 mg/l (RIFM, 2011).

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

The 96-h LC50 of benzyl acetate in juvenile Japanese medaka (*Oryzias laptipes*) fish was 4.00 mg/l (Holcombe et al., 1995).

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

9.2.4. Other available data

Benzyl acetate has been registered for REACH and a full dossier with additional data is available (accessed 9/30/13) A 48 h *daphnia magna* acute study following the OECD 202 guidelines was reported. EC50 was reported to be 17 mg/l. A 72 h algae inhibition test was conducted according to the OECD 201 method. The following EC50s were reported: 110 mg/l and 92 mg/l for growth rate and biomass, respectively.

9.2.5. Risk assessment refinement

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

9.2.6. Literature Search and Risk Assessment Completed on:

09/16/13.

10. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L). Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	202.5 mg/l			1,000,000	0.2025 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** **Ver 1.11**	18.01mg/l	37.11 mg/l	15.59 mg/l	10,000	1.559 μg/l	Esters
ECOSAR Acute Endpoints **(Tier 2)** **Ver 1.11**	104.36 mg/l	59.70 mg/l	45.86 mg/l			Neutral Organics
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	4.0 mg/l		0.92 mg/l	100	9.2 μg/l	
Daphnia		17 mg/l				
Algae		92 mg/l				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.0	2.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	>1000	>1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 9.2 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

- **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.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.07.010.

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