Short review

RIFM fragrance ingredient safety assessment, \( \alpha \)-Methylbenzyl acetate, CAS Registry Number 93-92-5

A.M. Api \( \textsuperscript{a}, \textsuperscript{*} \), D. Belsito \( \textsuperscript{b} \), S. Bhatia \( \textsuperscript{a} \), M. Bruze \( \textsuperscript{c} \), P. Calow \( \textsuperscript{d} \), M.L. Dagli \( \textsuperscript{e} \), W. Dekant \( \textsuperscript{f} \), A.D. Fryer \( \textsuperscript{g} \), L. Kromidas \( \textsuperscript{a} \), S. La Cava \( \textsuperscript{a} \), J.F. Lalko \( \textsuperscript{a} \), A. Lapczynski \( \textsuperscript{a} \), D.C. Liebler \( \textsuperscript{h} \), V.T. Politano \( \textsuperscript{a} \), G. Ritacco \( \textsuperscript{a} \), D. Salvito \( \textsuperscript{a} \), T.W. Schultz \( \textsuperscript{i} \), J. Shen \( \textsuperscript{a} \), I.G. Sipes \( \textsuperscript{j} \), B. Wall \( \textsuperscript{a} \), D.K. Wilcox \( \textsuperscript{a} \)

\( \textsuperscript{a} \) Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA
\( \textsuperscript{b} \) Columbia University Medical Center, Department of Dermatology, 616 Fort Washington Ave., New York, NY, 10032, USA
\( \textsuperscript{c} \) Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden
\( \textsuperscript{d} \) Humphrey School of Public Affairs, University of Minnesota, 301 15th Avenue South, Minneapolis, MN, 55455, USA
\( \textsuperscript{e} \) University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP, 05508-900, Brazil
\( \textsuperscript{f} \) University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany
\( \textsuperscript{g} \) Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA
\( \textsuperscript{h} \) Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37222-0146, USA
\( \textsuperscript{i} \) The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA
\( \textsuperscript{j} \) Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

* Corresponding author.
E-mail address: AAPi@rifm.org (A.M. Api).

A B S T R A C T

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. Developmental toxicity was determined to have the most conservative systemic exposure derived NO\( \text{A}\)EL of 100 mg/kg/day. A gavage developmental toxicity study conducted in rats on a suitable read across analog resulted in a MOE of 3571 while considering 78.7% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

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1. Identification

1. Chemical Name: \( \alpha \)-Methylbenzyl acetate
2. CAS Registry Number: 93-92-5
3. Synonyms: \( \alpha \)-Methylbenzyl acetate, Benzenemethanol, \( \alpha \)-methyl-, acetate, Gardenol, Methylphenylcarbinyl acetate, sec-Phenylethyl acetate, \( \alpha \)-Phenylethyl acetate, Phenyl methyl carbinyl acetate, Styralyl acetate, 3,4-Methyl(\( \text{C} = 1-5 \)) phenyl-2,3-dihydro-2H-1-benzopyran-7-one, 1-Phenylethyl acetate
4. Molecular Formula: \( \text{C}_{10}\text{H}_{12}\text{O}_{2} \)
5. Molecular Weight: 164.2
6. RIFM Number: 178

2. Physical data

1. Boiling Point: 214 °C [FMA database], 223.12 °C [EPI Suite]
2. Flash Point: 195 °F; CC [FMA database]
3. \( \log K_{\text{OW}} \): 2.5 at 30 °C [RIFM, 1996b], 2.5 [EPI Suite]
4. Melting Point: −0.17 °C [EPI Suite]
Water Solubility: 481.1 mg/L [EPI Suite]

Specific Gravity: 1.023–1.026 [FMA database], 1.025–1.028 [FMA], 1.0241 [RIFM Database], 1.03 g/ml [RIFM, 1994], 1.023–1.026 @ 25/25 °C [Gaunt et al., 1974]

Vapor Pressure: 5.5 Pa at 20 °C [RIFM, 2011], 0.0733 mm Hg @ 20 °C [EPI Suite 4.0], 0.1 mm Hg 20 °C [FMA database], 0.112 mm Hg @ 25 °C [EPI Suite]

UV Spectra: No significant absorption in the region of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ cm⁻¹).

Appearance/Organoleptic: A clear, colorless to pale yellow liquid, having an intense green odor suggesting gardenia.
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. Developmental toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 100 mg/kg/day. A gavage developmental toxicity study conducted in rats on a suitable read across analog resulted in a MOE of 3571 while considering 78.7% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

**Human Health Safety Assessment**

- **Genotoxicity:** Not genotoxic
- **Repeated Dose Toxicity:** NOAEL = 150 mg/kg/day (Tennant et al., 1987; Shelby et al., 1993)
- **Developmental and Reproductive Toxicity:** (Gaunt et al., 1974)
- **Skin Sensitization:** Not sensitizing
- **Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergic
- **Local Respiratory Toxicity:** NOAEC = 10 ppm or 61.4 mg/L

**Environmental Safety Assessment**

- **Persistence:** Critical Measured Value: 1.2% (IFRA, 2008)
- **Bioaccumulation:** Screening Level: 20.68 L/kg (EpiSuite ver 4.1)
- **Ecotoxicity:** Critical Ecotoxicity Endpoint: 96 h fish (Brachydanio rerio) LC50: 21.0 mg/L
- **Hazard Assessment:** Not PBT as per IFRA Environmental Standards
- **Risk Assessment:** Screening-Level: PEC/PNEC (North America and Europe) > 1
- **Critical Ecotoxicity Endpoint:** 96 h fish (Brachydanio rerio) LC50: 21.0 mg/L
- **RIFM PNEC is:** 3.66 µg/L

**Revised PEC/PNECs (2011 IFRA VolU):** North America and Europe <1

3. **Exposure**

| 1. Volume of Use (worldwide band): | >1000 metric tons per year | (IFRA, 2011) |
| 2. Average Maximum Concentration in Hydroalcoholics: | 1.2% | (IFRA, 2008) |
| 3. 97.5th Percentile: | 1.28% | (IFRA, 2008) |
| 4. Dermal Exposure*: | 0.0326 mg/kg/day | (IFRA, 2008) |
| 5. Oral Exposure: | Not available | |
| 6. Inhalation Exposures**: | 0.002 mg/kg/day | (IFRA, 2008) |
| 7. Total Systemic Exposure (Dermal + Inhalation): | (0.0326 mg/kg/day × 78.7% absorption) + 0.002 mg/kg/day = 0.028 mg/kg/day | |

*Calculated using the reported 97.5th 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 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. **Derivation of systemic absorption**

1. **Dermal:** 78.7%, read-across from benzyl acetate (CAS # 140-11-4) 
   Bronaugh et al., 1990: The skin absorption of read across material [7-14C] benzyl acetate (CAS # 104-11-1; see Section 5) was measured in 4 female rhesus monkeys. The test material in acetone was applied at a concentration of 4 µg/cm² to a 1 cm² 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 14C-equivalents excreted in the urine over the 5 day collection period. When the application site was occluded with either plastic wrap or a glass chamber, the absorption of benzyl acetate was 17.3 ± 2.7% and 78.7 ± 7.5%, respectively. When the site was not occluded, the absorption was 34.6 ± 9.4%.
2. **Oral:** Data not available — not considered.
3. **Inhalation:** Assumed 100%
4. **Total:** Dermal (78.7%) + Inhalation (assume 100%) absorbed = (0.0326 mg/kg/day × 78.7%) + 0.002 mg/kg/day = 0.028 mg/kg/day
5. Computational toxicology evaluation

1 Cramer Classification: Class I, Low

<table>
<thead>
<tr>
<th>Expert judgment</th>
<th>Toxtree v 2.6</th>
<th>OECD QSAR Toolbox v 3.2</th>
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2 Analogues Selected:
- a) Genotoxicity: Benzyl acetate (CAS # 140-11-4)
- b) Repeated Dose Toxicity: benzyl acetate (CAS # 140-11-4)
- c) Developmental and Reproductive Toxicity: Benzyl acetate (CAS # 140-11-4)
- d) Skin Sensitization: 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

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

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

α-Methylbenzyl acetate is reported to occur in the following foods:
- Avocado (Persea americana Mill.)
- Guava and Feyoa
- Strawberry guava (Psidium cattleianum Sabine)

8. IFRA standard

None.

9. REACH dossier

Available; accessed on 04/23/14.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1. Risk assessment. α-Methylbenzyl acetate was tested by the BlueScreen assay and was found negative for both cytotoxicity and genotoxicity indicating a lack of genotoxic potential (RIFM, 2013a). There are no studies assessing the mutagenic potential of α-methylbenzyl acetate, however, read across can be made to benzyl acetate (CAS # 140-11-4; See Section 5) which was assessed for mutagenicity in an Ames study similar to OECD TG 471 using the plate incorporation method. S. typhimurium strains TA98, TA100, TA1535, and TA1537 were exposed to concentrations of benzyl acetate up to 10 mg per plate in the presence and absence of liver S-9 fractions. No significant increases in revertant colonies were seen with benzyl acetate with or without metabolic activation (S9). The study concluded that benzyl acetate is not mutagenic under the conditions of this test (Tennant et al., 1987)

There are no studies assessing the clastogenic activity of α-methylbenzyl acetate. The clastogenic potential of read across analog benzyl acetate was assessed in several in vitro mouse lymphoma cell assays with and without metabolic activation with varying results. However, several in vivo studies assessing the effect of the material on inducing chromosomal aberrations, unscheduled DNA synthesis, demonstrate that benzyl acetate lacks genotoxic potential (NTP, 1993; Steinmetz and Mirsalis, 1984). In an in vivo mammalian erythrocyte micronucleus assay performed in equivalence to or similar to OECD TG 474, groups of 5–7 male mice were administered benzyl acetate in corn oil via intraperitoneal injection for 3 consecutive days at doses up to 1250 mg/kg. No genotoxic activity was observed, and the material was considered not clastogenic (Shelby et al., 1993)

Taken together, benzyl acetate does not present a concern for genotoxic potential and this can be extended to α-methylbenzyl acetate.

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

Literature Search and Risk Assessment Completed on: 05/07/14.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. The repeated dose toxicity data on α-methylbenzyl acetate are sufficient for the repeated dose toxicity endpoint. A gavage 13-week subchronic toxicity study conducted in rats determined the NOAEL to be 150 mg/kg/day, the highest dosage tested (Gaunt et al., 1974). Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 150/0.028 or 5357.

Additional References: McGinty et al., 2012a; Belsito et al., 2012; McGinty et al., 2012b; McGinty et al., 2012c; 2012d; McGinty, 2012e; RIFM, 2013b; RIFM, 1986b; RIFM, 1957; Abdo and Wenk, 1995; Abdo et al., 1998; Longnecker et al., 1986, 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;
in body weight. These data indicate no specific toxicity for rats up to the high dosage of 4500 mg/kg/day. Lengthening of the highest dose level were most likely a developmental toxicity study that was conducted in rats. The NOAEL for developmental toxicity was determined 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 benzyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.028 or 3571.

There are no reproductive toxicity data on α-methylbenzyl acetate. Read across material benzyl acetate (CAS # 140-11-4; see Section 5) has a gavage developmental toxicity study conducted in rats. The NOAEL for developmental toxicity was determined to be 500 mg/kg/day based on weight gain and the fetal NOAEL was 100 mg/kg/day based on weight and internal organ malformations.

Risk assessment. There are no developmental toxicity data on α-methylbenzyl acetate. Read across material benzyl acetate (CAS # 140-11-4) has a gavage developmental toxicity study conducted in rats that determined the NOAEL for maternal 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 benzyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.028 or 17857.

RIFM's Expert Panel* and the adjunct Reproduction Advisory Group reviewed the 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.


Literature Search and Risk Assessment Completed on: 05/02/2014.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for α-methylbenzyl acetate 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 α-methylbenzyl acetate. Read across material benzyl acetate (CAS # 140-11-4; see Section 5) has a gavage developmental toxicity study that was conducted in rats. The NOAEL for developmental toxicity was determined 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 benzyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.028 or 17857.

There are no reproductive toxicity data on α-methylbenzyl acetate. Read across material benzyl acetate (CAS # 140-11-4) has a gavage developmental toxicity study conducted in rats that determined the NOAEL for maternal toxicity to be 500 mg/kg/day, based on maternal body weight gain (Ishiguro et al., 1993). In 13-week dietary subchronic toxicity studies in rats and mice with benzyl acetate, sperm morphology and vaginal cytology examinations were evaluated (Morrisey et al., 1988; NTP, 1993). 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 benzyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.028 or 17857.
10.1.6. Local respiratory toxicity

The margin of exposure for \( \alpha \)-methylbenzyl acetate is adequate for the respiratory endpoint at the current level of use.

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. There are no inhalation data available on \( \alpha \)-methylbenzyl acetate. A NOAEC of 10 ppm (61.4 mg/m\(^3\)) is reported for read across analog, benzyl acetate (CAS # 140-11-4; see Section 5), for a 2 week acute study conducted in rats (RIFM, 2013b). At this level, increased lactate dehydrogenase was 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, the lower exposure dose (61.4 mg/m\(^3\)) was considered.

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

- \((61.4 \text{mg/m}^3)(1 \text{m}^3/1000 \text{L}) = 0.0614 \text{mg/L}\)
- Minute ventilation (MV) of 0.17 L/min for a Sprague–Dawley rat \( \times \) duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- \((0.0614 \text{mg/L})(61.2 \text{L/d}) = 3.76 \text{mg/d}\)
- \((3.76 \text{mg/d})/(0.0016 \text{kg lung weight of rat}^*) = 2349 \text{mg/kg lw/day}\)

Based on the IFRA survey results for hydroalcoholics the 97.5th percentile was reported to be 1.28%. Assuming 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 0.12 mg/day as calculated using RIFM’s 2-Box models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual. 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 0.181 mg/kg lung weight/day resulting in a MOE of 129,765 (i.e., \([2349 \text{mg/kg lw/day}]/[0.181 \text{mg/kg lung weight/day}]\)). The MOE is significantly greater than 100. Without the adjustment for specific uncertainty factors related to inter-species and intra-species variation the material exposure by inhalation at 1.28% in a combination of the products noted above is deemed to be safe under the most conservative consumer exposure scenario.

Additional References: RIFM, 1997; RIFM, 1997b; Silver, 1992; RIFM, 1997a; Isola et al., 2003a; RIFM, 2003b; Rogers et al., 2003; 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.


10.2.1. Screening-level assessment

A screening level risk assessment of \( \alpha \)-methylbenzyl acetate 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 2, 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, \( \alpha \)-methylbenzyl 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 \( \alpha \)-methylbenzyl acetate 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 EPISUITE ver 4.1). 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), \( \alpha \)-methylbenzyl acetate presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 1994: The ready and ultimate biodegradability of \( \alpha \)-methylbenzyl acetate was determined by a CO\(_2\) production test based on OECD Guideline 301B. \( \alpha \)-Methylbenzyl acetate at 10 mg/l organic carbon was directly added to the incubation mixture, and incubated for 28 days. Biodegradation was 106.0% (102.3%–109.6%).

RIFM, 1996: The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test following the OECD 301F method. Under the conditions of this study, biodegradation of 89% was observed.

RIFM, 1993: The biodegradation potential of the test material was measured using the CO\(_2\) evolution method following the OECD 301B guidelines. After 28 days of incubation, a biodegradation of 65% was observed.

10.2.3.2. Ecotoxicity. RIFM, 1993: A 96 h acute fish (Brachydanio rerio) toxicity test was conducted with the test material. Under conditions of the study the LC\(_0\), LC\(_50\) and LC\(_100\) were determined to be 15.0, 21.0 and 28.5 mg/l, respectively.

10.2.3.3. Other available data. \( \alpha \)-Methylbenzyl acetate has been registered under REACH, however no additional data is available.

11. Risk assessment refinement

In the REACH dossier PNEC has been calculated using the same key study (fish acute) as in this document, but since read – across data for additional endpoints is also included the Assessment Factor is lower (1000 vs 5000). Ecotoxicological data and PNEC derivation (all endpoints...
Endpoints used to calculate PNEC are underlined. Exposures and PEC calculation (following RIFM Framework: Salvito et al., 2002).

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

The RIFM PNEC is 3.66 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.

Literature Search and Risk Assessment Completed on: 5/06/14.

12. Literature Search*

- RIFM database: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHA: http://echa.europa.eu/
- OECD Toolbox
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- OECD SIDS: http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- EPA Actor: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B79062229F477472A9A4D05B7
- US EPA Robust Summary: http://cfpub.epa.gov/HPVIS/summary.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=KMS0UpiQKarsQS324GwB&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.2016.01.020.

### Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.01.020.

<table>
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<th>Target material</th>
<th>Read across material</th>
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<tr>
<td>Principal Name</td>
<td>Benzyl acetate</td>
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<tr>
<td>CAS No.</td>
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### 3D Structure

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<tr>
<td>Molecular Weight:</td>
<td>164.21 g/mol</td>
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<tr>
<td>Melting Point (°C)</td>
<td>234.30</td>
</tr>
<tr>
<td>Boiling Point (°C)</td>
<td>150.17</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>0.0624 mmHg</td>
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<tr>
<td>Log K&lt;sub&gt;ow&lt;/sub&gt; (mmHg @ 25°C)</td>
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### Skin Absorption

- **Skin Absorption Percentage (SAM)**: 80%
- **Skin Abosorption**: 80%
- **DNA binding by OASIS v 1.1 Q SAR Tool Box (3.1)**
  - Schiff base formers
  - Schiff base formers >> Direct acting Schiff base formers
  - Schiff base formers >> Direct acting Schiff base formers >> Specific Acetate Esters
  - SN1
  - SN1 >> Carbenium ion formation
  - SN1 >> Carbenium ion formation >> Specific Acetate Esters
  - SN2
  - SN2 >> Acylating agents
  - SN2 >> Acylating agents >> Specific Acetate Esters
  - SN2 >> SN2 at sp3-carbon atom
  - SN2 >> SN2 at sp3-carbon atom >> Specific Acetate Esters
  - 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
  - No alerts

### DNA binding OECD

- Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals
- Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals >> Arenes
- No alerts

### Carcinogenicity (genotoxic and non-genotoxic) alerts by ISS

- Schiff base formers
- Schiff base formers >> Direct acting Schiff base formers
- Schiff base formers >> Direct acting Schiff base formers >> Specific Acetate Esters
- SN1
- SN1 >> Carbenium ion formation
- SN1 >> Carbenium ion formation >> Specific Acetate Esters
- SN2
- SN2 >> Acylating agents
- SN2 >> Acylating agents >> Specific Acetate Esters
- SN2 >> SN2 at sp3-carbon atom
- SN2 >> SN2 at sp3-carbon atom >> Specific Acetate Esters
- No alerts

### DNA alerts for Ames, MN, CA by OASIS v 1.1

- Schiff base formers
- Schiff base formers >> Direct acting Schiff base formers
- Schiff base formers >> Direct acting Schiff base formers >> Specific Acetate Esters
- SN1
- SN1 >> Carbenium ion formation
- SN1 >> Carbenium ion formation >> Specific Acetate Esters
- SN2
- SN2 >> Acylating agents
- SN2 >> Acylating agents >> Specific Acetate Esters
- SN2 >> SN2 at sp3-carbon atom
- SN2 >> SN2 at sp3-carbon atom >> Specific Acetate Esters
- No alerts

### In-vitro Mutagenicity (Ames test) alerts by ISS

- H-acceptor-path3-H-acceptor
In-vivo mutagenicity (Micronucleus) alerts by ISS
- Not classified

Oncologic Classification
- Not classified

Reproductive and Developmental toxicity
- Non toxicant (low reliability)

Developmental Toxicity Model by CAESAR v2.1.6
- Non binder

ER Binding by OECD QSAR Toolbox (3.1)
- Non binder

Skin sensitization
- Sensitizer (low reliability)

Protein binding by OASIS v1.1
- SN2
- SN2 >> Nucleophilic substitution at sp3 Carbon atom
- SN2 >> Nucleophilic substitution at sp3 Carbon atom >> Activated alkyl esters

Protein binding by OECD
- SN2
- SN2 >> SN2 reaction at sp3 carbon atom
- SN2 >> SN2 reaction at sp3 carbon atom >> Allyl acetates and related chemicals
- SN2 >> SN2 reaction at sp3 carbon atom >> Activated alkyl esters

Protein binding potency
- Not possible to classify according to these rules (GSH)

Protein binding alerts for skin sensitization by OASIS v1.1
- SN2
- SN2 >> Nucleophilic substitution at sp3 Carbon atom
- SN2 >> Nucleophilic substitution at sp3 Carbon atom >> Activated alkyl esters

Skin Sensitization model (CAESAR) (version 2.1.5)
- Sensitizer (low reliability)

Metabolism
- Not possible to classify according to these rules (GSH)

OECD QSAR Toolbox (3.1)
- Activated alkyl esters
- Nucleophilic substitution at sp3 Carbon atom
- SN2
- SN2 reaction at sp3 carbon atom
- SN2 reaction at sp3 carbon atom >> Allyl acetates and related chemicals
- SN2 reaction at sp3 carbon atom >> Activated alkyl esters
- SN2 reaction at sp3 carbon atom >> GSH

Rat liver S9 metabolism simulator
- Not possible to classify according to these rules (GSH)

1 Values calculated using Pipeline Pilot with FCFP fingerprint (Rogers and Hahn, 2010).

Appendix B.

Summary:
There are insufficient toxicity data on alpha-methylbenzyl acetate (RIFM# 178, CAS# 93-92-5). Hence, in silico evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods:
- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analog were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/Rationale
- Benzyl acetate (analog) was used as a read-across for alpha-methylbenzyl acetate (target) based on:
  o The target and analog belong to the generic class of aromatic esters, specifically, esters/aryl alkyl alcohol simple acid/ benzylic alcohol.
  o The target and analog have the same carboxylic acid part and similar alcohol part.
  o The only difference is that the target has a methyl group attached to the alpha carbon in the alcohol part. The difference between structures does not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, their toxicology profiles are expected to be similar.
  o The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  o The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  o The target and analog show similar alerts for protein binding.
  o The target and analog are expected to be metabolized similarly. As per the OECD Toolbox they are predicted to have similar metabolites.

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