

## Short review

## RIFM fragrance ingredient safety assessment, 4-methylbenzyl acetate, CAS Registry Number 2216-45-7



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## ARTICLE INFO

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## 1. Identification

- Chemical Name:** 4-Methylbenzyl acetate
- CAS Registry Number:** 2216-45-7
- Synonyms:** 4-Methylbenzyl acetate, p-Acetoxyethyltoluene, Benzenemethanol, 4-methyl-, acetate, p-Methylbenzyl acetate, p-Tolubenzyl acetate, p-Xylyl acetate, 酢酸メチルベンジル
- Molecular Formula:** C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>
- Molecular Weight:** 164.2
- RIFM Number:** 1164

## 2. Physical data

- Boiling Point:** 222 °C [FMA database], 234.3 °C [EPI Suite]
- Flash Point:** >200 °F; CC [FMA database]

- Log Kow:** 2.63 [EPI Suite]
- Melting Point:** 16.86 °C [EPI Suite]
- Water Solubility:** 539.8 mg/L [EPI Suite]
- Specific Gravity:** 1.040 [FMA], 1.027–1.033 [RIFM database]
- Vapor Pressure:** 0.0404 mm Hg @ 20 °C [EPI Suite 4.0], 0.05 mm Hg @ 20 °C [FMA], 0.0624 mm Hg @ 25 °C [EPI Suite]
- UV Spectra:** No absorption in the region 290–400 nm; molar absorption coefficient is below the benchmark (1000 L mol<sup>-1</sup> · cm<sup>-1</sup>).
- Appearance/Organoleptic:** A colorless liquid with a sweet, floral-fruity and mildly green-herbaceous odor.

## 3. Exposure

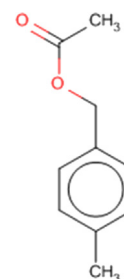
- Volume of Use (worldwide band):** <1 metric tons per year (IFRA, 2011)
- Average Maximum Concentration in Hydroalcohols:** 0.15% (IFRA, 2008)
- 97.5th Percentile:** 0.57% (IFRA, 2008)
- Dermal Exposure<sup>1</sup>:** 0.0146 mg/kg/day (IFRA, 2008)
- Oral Exposure:** Not available
- Inhalation Exposures<sup>2</sup>:** 0.00088 mg/kg/day (IFRA, 2008)
- Total Systemic Exposure (Dermal + Inhalation):** (0.0146 mg/kg/day × 78.7% absorption) + 0.00088 mg/kg/day = 0.012 mg/kg/day

<sup>1</sup> Calculated using the reported 97.5th percentile concentration

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Version: 030816. This version replaces any previous versions.  
 Name: 4-Methylbenzyl acetate  
 CAS Registry Number: 2216-45-7



#### 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 the RIFM Criteria Document Api et al., 2015 which 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, as well as environmental safety. Data from the suitable read across analog, Benzyl acetate (CAS# 140-11-4) show that this material is not genotoxic nor does it have skin sensitization potential. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using Benzyl acetate (CAS# 140-11-4) as a suitable read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

#### Human Health Safety Assessment

**Genotoxicity:** Not genotoxic. (Tennant et al., 1987; Shelby et al., 1993)

**Repeated Dose Toxicity:** NOAEL = 14.5 mg/kg/day (NTP, 1993)

**Developmental and Reproductive Toxicity:** NOAEL = 100 mg/kg/day (Ishiguro, 1993)

**Skin Sensitization:** Not sensitizing (RIFM, 1988a; RIFM, 1988b; RIFM, 1988c; RIFM, 1988d; RIFM, 1985a; RIFM, 1985b; RIFM, 1985c; RIFM, 1986a; RIFM, 1981; RIFM, 1961; RIFM, 1985a,b,c; Greif, 1967; RIFM, 1975a; RIFM, 1975b; RIFM, 1975c; RIFM, 1975d; RIFM, 1975e; Klecak, 1985)

**Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergenic (UV Spectra, RIFM Database)

**Local Respiratory Toxicity:** NOAEC = 10 ppm or 61.4 mg/m<sup>3</sup> (0.0614 mg/L) (RIFM, 2013b)

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**Environmental Safety Assessment****Hazard Assessment:****Persistence:** Screening Level: 2.9017 (BIOWIN 3) (EpiSuite ver 4.1)**Bioaccumulation:** Screening Level: 18.92 L/kg (EpiSuite ver 4.1)**Ecotoxicity:** Screening Level: LC50: 62.7 mg/L (Salvito et al., 2002)**Conclusion:** Not PBT as per IFRA Environmental Standards**Risk Assessment:****Screening-Level:** PEC/PNEC (North America and Europe) (Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 62.7 mg/L (Salvito et al., 2002)

**RIFM PNEC is:** 0.0627 µg/L

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; Cleared at screening level

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).

<sup>2</sup>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%

Bronaugh et al., 1990: The skin absorption of read across material [<sup>14</sup>C] benzyl acetate (CAS # 104-11-1; see Section V) was measured in 4 female rhesus monkeys. The test material in acetone was applied at a concentration of 4 µg/cm<sup>2</sup> to a 1 cm<sup>2</sup> 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 <sup>14</sup>C-equivalents excreted in the urine over the 5 day collection period. When the application site was occluded with either plastic wrap or a glass chamber, the absorption of benzyl acetate was 17.3 ± 2.7% and 78.7 ± 7.5%, respectively. When the site was not occluded, the absorption was 34.6 ± 9.4%.

**2. Oral:** Data not available – not considered.**3. Inhalation:** Assumed 100%

**4. Total:** Dermal (78.7%) + Inhalation (assume 100%) absorbed = (0.0146 mg/kg/day × 78.7%) + 0.00088 mg/kg/day = 0.012 mg/kg/day

**5. Computational toxicology evaluation**

1. Cramer Classification: Class I, Low

Expert judgment	Toxtree v 2.6	OECD QSAR toolbox v 3.2
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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:** Nonef. **Local Respiratory Toxicity:** Benzyl acetate (CAS # 140-11-4)g. **Environmental Toxicity:** None3. **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)**

4-Methylbenzyl acetate has not been reported to occur in food by the VCF\*.

\*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**

Pre-Registered for 2010; No dossier available as of 03/8/2016.

**10. Summary****10.1. Human Health Endpoint Summaries****Genotoxicity:**

Based on the current existing data and use levels, 4-methylbenzyl acetate does not present a concern for genetic toxicity.

**Risk Assessment:**

4-Methylbenzyl acetate was tested in 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 4-methylbenzyl acetate however, read across can be made to benzyl acetate (CAS # 140-11-4; see Section V) which has been assessed for mutagenicity in an Ames study. The mutagenic potential of benzyl acetate was

assessed by an Ames test 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/plate in the presence and absence of liver S-9 fractions. No substantial 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 the study (Tennant et al., 1987).

The clastogenic potential of 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 material's effects on inducing chromosomal aberrations and 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 B6C3F1 mice were administered benzyl acetate in corn oil via intraperitoneal injection for 3 consecutive days at doses up to 600 mg/kg. No genotoxic activity was observed and the material was considered to be not clastogenic (Shelby et al., 1993).

Taken together, benzyl acetate does not present a concern for genotoxic potential and this can be extended to 4-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., 1983, 1989; Steinmetz and Mirsalis, 1984; Foureman et al., 1994; Matsuoka et al., 1996; Yoshikawa, 1996; Miyagawa et al., 1995; Mitchell and Caspary, 1987; Zimmermann et al., 1989; Honma et al., 1999; Kevekordes et al., 1999, 2001; Rossman et al., 1991; Sekihashi et al., 2002; Yoo, 1985; Demir et al., 2010; Scott et al., 2007; Yasunaga et al., 2004; Witt et al., 2000; Sasaki, 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: 05/06/14.

#### Repeated dose toxicity:

The margin of exposure for 4-methylbenzyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

#### Risk Assessment:

There are no repeated dose toxicity data on 4-methylbenzyl acetate. Read across material benzyl acetate (CAS # 140-11-4; see Section V) has numerous oral repeated dose toxicity studies conducted 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 benzyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 14.5/0.012 or 1208.

**Additional References:** McGinty et al., 2012a, 2012b; Belsito et al., 2012; 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; Grundschober, 1977; Miyashita and Robinson, 1980; Chidgey and Caldwell, 1986; Chidgey et al., 1987; McMahan et al., 1989a; Augustinsson and Ekedahl, 1962; Clapp and Young, 1970; McMahan et al., 1989b; Schunk et al., 1986; Hotchkiss et al., 1989, 1992b; Caldwell et al., 1987; Hotchkiss, 1998; Hotchkiss et al., 1992c; Meyer, 1965; Garnett et al., 1994; Jimbo, 1983; Hotchkiss et al., 1988, 1990a,b, 1992d; RIFM, 1989a; RIFM, 1989b; McGinty et al., 2012c.

Literature Search and Risk Assessment Completed on: 04/29/14.

#### Developmental and Reproductive Toxicity:

The margin of exposure for 4-methylbenzyl acetate is adequate

for the developmental and reproductive toxicity endpoints at the current level of use.

#### Risk Assessment:

There are no developmental toxicity data on 4-methylbenzyl acetate. Read across material benzyl acetate (CAS # 140-11-4; see Section V) 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, 100/0.012 or 8333.

There are no reproductive toxicity data on 4-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 (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 benzyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 500/0.012 or 41,667.

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.

**Additional References:** McGinty et al., 2012a, 2012b; Belsito et al., 2012; 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; Grundschober, 1977; Miyashita and Robinson, 1980; Chidgey and Caldwell, 1986; Chidgey et al., 1987; McMahan et al., 1989a; Augustinsson and Ekedahl, 1962; Clapp and Young, 1970; McMahan et al., 1989b; Schunk et al., 1986; Hotchkiss et al., 1989, 1992b; Caldwell et al., 1987; Hotchkiss, 1998; Hotchkiss et al., 1992c; Meyer, 1965; Garnett et al., 1994; Jimbo, 1983; Hotchkiss et al., 1988, 1990a,b, 1992d; RIFM, 1989a; RIFM, 1989b; McGinty et al., 2012c.

Literature Search and Risk Assessment Completed on: 04/29/14.

#### Skin Sensitization:

Based on existing material specific data and read across to benzyl acetate (CAS# 140-11-4); 4-methylbenzyl acetate does not present a concern for skin sensitization.



**Risk Assessment:**

Based on existing material specific data and read across to benzyl acetate (CAS# 140-11-4; see Section V); 4-methylbenzyl acetate does not present a concern for skin sensitization. While the chemical structure of these materials indicates that they would be expected to react with skin proteins, the reactivity would be 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 to benzyl acetate (RIFM, 1985a; RIFM, 1985b; RIFM, 1986a; RIFM, 1985c; Klecak, 1985). Additionally, no reactions indicative of skin sensitization were observed in both the human repeated insult patch test and the human maximization test to benzyl acetate (RIFM, 1975a; RIFM, 1975b; RIFM, 1975c; RIFM, 1975d; RIFM, 1975e; RIFM, 1988a; RIFM, 1988b; RIFM, 1988c; RIFM, 1988d; RIFM, 1961; Greif, 1967; RIFM, 1987). Finally, in the human maximization test no reactions indicative of skin sensitization were observed to 4-methylbenzyl acetate (RIFM, 1981).

Additional References: None.

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

**Phototoxicity/Photoallergenicity:**

Based on UV absorption spectra, 4-methylbenzyl acetate does not present a concern for phototoxicity or photoallergenicity.

**Risk Assessment:**

There are no phototoxicity studies available for 4-methylbenzyl acetate in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity,  $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$  (Henry et al., 2009). Based on lack of absorbance, 4-methylbenzyl acetate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/21/15.

**Local Respiratory Toxicity:**

The margin of exposure for 4-methylbenzyl acetate is adequate for the respiratory endpoint at the current level of use.

**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. A NOAEC of 10 ppm ( $61.4 \text{ mg/m}^3$ ) is reported for read across material, benzyl acetate (CAS # 140-11-4; see Section V), for a 2 week acute study conducted in rats (RIFM, 2013b). Test substance-related higher bronchoalveolar lavage fluid lactate dehydrogenase values were noted in the  $614 \text{ mg/m}^3$  group males and females when compared to the control group.

This NOAEC expressed in  $\text{mg/kg}$  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 X 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 hydroalcohols, the 97.5th percentile was reported to be 0.57%. 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 0.053 mg/day as calculated based on the IFRA survey results for the 97.5th percentile use in hydroalcohols for a 60 kg

individual using RIFM's 2-Box/MPPD *in silico* models. To compare this estimated exposure with the NOAEC expressed in  $\text{mg/kg}$  lung weight/day this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give  $0.082 \text{ mg/kg}$  lung weight/day resulting in a MOE of 286,432 (i.e.,  $[23,487.5 \text{ mg/kg lw/day}] / [0.082 \text{ mg/kg lung weight/day}]$ ).

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 0.57% in a combination of the products noted above is deemed to be safe under the most conservative consumer exposure scenario.

**Additional References:** RIFM, 1977; RIFM, 1997b; Silver, 1992; RIFM, 1997a; Rogers et al., 2003; RIFM, 2003b; RIFM, 2003a; Isola et al., 2003; 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.

Literature Search and Risk Assessment Completed on: 05/09/14.

**10.2. Environmental Endpoint Summary****Screening-Level Assessment:**

A screening level risk assessment of 4-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 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, 4-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 4-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 I.

**Risk Assessment:**

Based on current volume of use (2011), 4-methylbenzyl acetate does not present a risk to the aquatic compartment in the screening level assessment.

**Key Studies:**

**Biodegradation:** No data available.

**Ecotoxicity:** No data available.

**Other available data:** 4-Methylbenzyl acetate has been pre-registered for REACH with no additional data at this time.

**Risk assessment refinement:**

Ecotoxicological data and PNEC derivation (all endpoints reported in  $\text{mg/L}$ ; PNECs in  $\mu\text{g/L}$ ).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level (Tier 1)	62.7 mg/L			1,000,000	0.0627 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log $K_{ow}$ used	2.63	2.63
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
<b>Risk Characterization: PEC/PNEC</b>	<b>&lt;1</b>	<b>&lt;1</b>

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

**The RIFM PNEC is 0.0627 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: 4/22/14.

## 11. 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](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/occdsids/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](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.

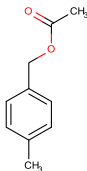
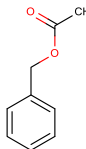
## Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2016.04.001>.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2016.04.001>.

## Appendix

	Target material	Read across material
<b>Principal Name</b>	4-Methylbenzyl acetate	Benzyl acetate
<b>CAS No.</b>	2216-45-7	140-11-4
<b>Structure</b>		
<b>3D Structure Endpoint</b>	<a href="http://www.thegoodscentscompany.com/opl/2216-45-7.html">http://www.thegoodscentscompany.com/opl/2216-45-7.html</a>	<a href="http://www.thegoodscentscompany.com/opl/140-11-4.html">http://www.thegoodscentscompany.com/opl/140-11-4.html</a>
<b>Molecular Formula:</b>	C10H12O2	C9H10O2
<b>Molecular Weight:</b>	164.2	150.17
<b>Melting Point (°C)</b>	16.86	-0.5
<b>Boiling Point (°C)</b>	234.30	215.57
<b>Vapor Pressure(mmHg @ 25 °C)</b>	0.0624	0.187

(continued on next page)

(continued)

	Target material	Read across material
<b>Log Kow (KOWWIN v1.68 estimate)</b>	2.63	2.08
<b>Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 estimate)</b>	539.8	1605
<b>J<sub>max</sub> (mg/cm<sup>2</sup>/h, RIFM SAM)</b>	70.7	64.0
<b>Henry's Law (Pa·m<sup>3</sup>/mol, Bond Method)</b>	1.58	1.4337
<b>Similarity (Tanimoto score)<sup>1</sup></b>		82%
<b>Genotoxicity</b>		
<b>DNA binding by OASIS v 1.1</b>	<ul style="list-style-type: none"> <li>• Schiff base formers</li> <li>• Schiff base formers &gt;&gt; Direct acting Schiff base formers</li> <li>• Schiff base formers &gt;&gt; Direct acting Schiff base formers &gt;&gt; Specific Acetate Esters</li> <li>• SN1</li> <li>• SN1 &gt;&gt; Carbenium ion formation</li> <li>• SN1 &gt;&gt; Carbenium ion formation &gt;&gt; Specific Acetate Esters</li> <li>• SN2</li> <li>• SN2 &gt;&gt; Acylating agents</li> <li>• SN2 &gt;&gt; Acylating agents &gt;&gt; Specific Acetate Esters</li> <li>• SN2 &gt;&gt; SN2 at sp3-carbon atom</li> <li>• SN2 &gt;&gt; SN2 at sp3-carbon atom &gt;&gt; Specific Acetate Esters</li> </ul>	<ul style="list-style-type: none"> <li>• Schiff base formers</li> <li>• Schiff base formers &gt;&gt; Direct acting Schiff base formers</li> <li>• Schiff base formers &gt;&gt; Direct acting Schiff base formers &gt;&gt; Specific Acetate Esters</li> <li>• SN1</li> <li>• SN1 &gt;&gt; Carbenium ion formation</li> <li>• SN1 &gt;&gt; Carbenium ion formation &gt;&gt; Specific Acetate Esters</li> <li>• SN2</li> <li>• SN2 &gt;&gt; Acylating agents</li> <li>• SN2 &gt;&gt; Acylating agents &gt;&gt; Specific Acetate Esters</li> <li>• SN2 &gt;&gt; SN2 at sp3-carbon atom</li> <li>• SN2 &gt;&gt; SN2 at sp3-carbon atom &gt;&gt; Specific Acetate Esters</li> </ul>
<b>DNA binding OECD</b>	<ul style="list-style-type: none"> <li>• Michael addition</li> <li>• Michael addition &gt;&gt; P450 Mediated Activation to Quinones and Quinone-type Chemicals</li> <li>• Michael addition &gt;&gt; P450 Mediated Activation to Quinones and Quinone-type Chemicals &gt;&gt; Arenes</li> </ul>	<ul style="list-style-type: none"> <li>• Michael addition</li> <li>• Michael addition &gt;&gt; P450 Mediated Activation to Quinones and Quinone-type Chemicals</li> <li>• Michael addition &gt;&gt; P450 Mediated Activation to Quinones and Quinone-type Chemicals &gt;&gt; Arenes</li> </ul>
<b>Carcinogenicity (genotox and non-genotox) alerts by ISS</b>	<ul style="list-style-type: none"> <li>• No alerts</li> </ul>	<ul style="list-style-type: none"> <li>• No alerts</li> </ul>
<b>DNA alerts for Ames, MN, CA by OASIS v 1.1</b>	<ul style="list-style-type: none"> <li>• Schiff base formers</li> <li>• Schiff base formers &gt;&gt; Direct acting Schiff base formers</li> <li>• Schiff base formers &gt;&gt; Direct acting Schiff base formers &gt;&gt; Specific Acetate Esters</li> <li>• SN1</li> <li>• SN1 &gt;&gt; Carbenium ion formation</li> <li>• SN1 &gt;&gt; Carbenium ion formation &gt;&gt; Specific Acetate Esters</li> <li>• SN2</li> <li>• SN2 &gt;&gt; Acylating agents</li> <li>• SN2 &gt;&gt; Acylating agents &gt;&gt; Specific Acetate Esters</li> <li>• SN2 &gt;&gt; SN2 at sp3-carbon atom</li> <li>• SN2 &gt;&gt; SN2 at sp3-carbon atom &gt;&gt; Specific Acetate Esters</li> </ul>	<ul style="list-style-type: none"> <li>• Schiff base formers</li> <li>• Schiff base formers &gt;&gt; Direct acting Schiff base formers</li> <li>• Schiff base formers &gt;&gt; Direct acting Schiff base formers &gt;&gt; Specific Acetate Esters</li> <li>• SN1</li> <li>• SN1 &gt;&gt; Carbenium ion formation</li> <li>• SN1 &gt;&gt; Carbenium ion formation &gt;&gt; Specific Acetate Esters</li> <li>• SN2</li> <li>• SN2 &gt;&gt; Acylating agents</li> <li>• SN2 &gt;&gt; Acylating agents &gt;&gt; Specific Acetate Esters</li> <li>• SN2 &gt;&gt; SN2 at sp3-carbon atom</li> <li>• SN2 &gt;&gt; SN2 at sp3-carbon atom &gt;&gt; Specific Acetate Esters</li> </ul>
<b>In-vitro Mutagenicity (Ames test) alerts by ISS</b>		
<b>In-vivo mutagenicity (Micronucleus) alerts by ISS</b>	<ul style="list-style-type: none"> <li>• H-acceptor-path3-H-acceptor</li> </ul>	<ul style="list-style-type: none"> <li>• H-acceptor-path3-H-acceptor</li> </ul>
<b>Oncologic Classification</b>	<ul style="list-style-type: none"> <li>• Not classified</li> </ul>	<ul style="list-style-type: none"> <li>• Not classified</li> </ul>
<b>Repeated dose toxicity</b>		
<b>Repeated Dose (HESS)</b>	<ul style="list-style-type: none"> <li>• Not categorized</li> </ul>	<ul style="list-style-type: none"> <li>• Not categorized</li> </ul>
<b>Developmental Toxicity</b>		
<b>Developmental Toxicity Model by CAESAR v2.1.6</b>	<ul style="list-style-type: none"> <li>• Non toxicant (low reliability)</li> </ul>	<ul style="list-style-type: none"> <li>• Toxicant (medium reliability)</li> </ul>
<b>ER Binding by OECD QSAR Toolbox (3.1)</b>	<ul style="list-style-type: none"> <li>• Non binder</li> </ul>	<ul style="list-style-type: none"> <li>• Non binder</li> </ul>
<b>Skin sensitization</b>		
<b>Protein binding by OASIS v1.1</b>	<ul style="list-style-type: none"> <li>• SN2</li> <li>• SN2 &gt;&gt; Nucleophilic substitution at sp3 Carbon atom</li> <li>• SN2 &gt;&gt; Nucleophilic substitution at sp3 Carbon atom &gt;&gt; Activated alkyl esters</li> </ul>	<ul style="list-style-type: none"> <li>• SN2</li> <li>• SN2 &gt;&gt; Nucleophilic substitution at sp3 Carbon atom</li> <li>• SN2 &gt;&gt; Nucleophilic substitution at sp3 Carbon atom &gt;&gt; Activated alkyl esters</li> </ul>
<b>Protein binding by OECD</b>	<ul style="list-style-type: none"> <li>• SN2</li> <li>• SN2 &gt;&gt; SN2 reaction at sp3 carbon atom</li> <li>• SN2 &gt;&gt; SN2 reaction at sp3 carbon atom &gt;&gt; Allyl acetates and related chemicals</li> </ul>	<ul style="list-style-type: none"> <li>• SN2</li> <li>• SN2 &gt;&gt; SN2 reaction at sp3 carbon atom</li> <li>• SN2 &gt;&gt; SN2 reaction at sp3 carbon atom &gt;&gt; Allyl acetates and related chemicals</li> </ul>
<b>Protein binding potency</b>	<ul style="list-style-type: none"> <li>• Not possible to quantify</li> </ul>	<ul style="list-style-type: none"> <li>• Not possible to quantify</li> </ul>
<b>Protein binding alerts for skin sensitization by OASIS v1.1</b>	<ul style="list-style-type: none"> <li>• SN2</li> <li>• SN2 &gt;&gt; Nucleophilic substitution at sp3 Carbon atom</li> <li>• SN2 &gt;&gt; Nucleophilic substitution at sp3 Carbon atom &gt;&gt; Activated alkyl esters</li> </ul>	<ul style="list-style-type: none"> <li>• SN2</li> <li>• SN2 &gt;&gt; Nucleophilic substitution at sp3 Carbon atom</li> <li>• SN2 &gt;&gt; Nucleophilic substitution at sp3 Carbon atom &gt;&gt; Activated alkyl esters</li> </ul>
<b>Skin Sensitization model (CAESAR) (version 2.1.5)</b>	<ul style="list-style-type: none"> <li>• Sensitizer (low reliability)</li> </ul>	<ul style="list-style-type: none"> <li>• Sensitizer (low reliability)</li> </ul>
<b>Metabolism</b>		
<b>OECD QSAR Toolbox (3.1)</b>	See Supplemental data 1	See Supplemental data 2
<b>Rat liver S9 metabolism simulator</b>		

<sup>1</sup> Values calculated using Pipeline Pilot with FCFP fingerprint. J. Chem. Inf. Model. 2010, 50: 742 (Rogers and Hahn, 2010).

## 12. Summary

4-Methylbenzyl acetate (RIFM# 1164, CAS# 2216-45-7) lacks toxicity data for the skin absorption, genotoxicity, repeated dose, developmental, reproductive, skin sensitization and phototoxicity/photoallergenicity and respiratory endpoints. Hence, *in silico* evaluation was conducted by determining suitable read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, benzyl acetate (RIFM# 106, CAS# 140-11-4) was identified as proper read-across for their respective toxicity endpoints.

## 13. Methods

- The identified read-across analog was 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)
- J<sub>max</sub> was calculated using RIFM skin absorption model (SAM) (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeated dose (HESS) were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity was estimated using CAESAR v2.1.6 (Cassano et al., 2010)
- Protein binding was estimated using OECD QSAR Toolbox (v 3.1) (OECD, 2012)
- Skin sensitization was estimated using CAESAR v 2.1.6 (Cassano et al., 2010)
- The major metabolites for the target and read-across analog were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

## 14. Conclusion/rationale

- Benzyl acetate (analog) was used as a read-across for 4-methylbenzyl acetate (target) based on:
  - The target and analog belong to the generic class of aromatic esters, specifically, esters/aryl alkyl alcohol simple acid/benzylic alcohol.
  - The target and analog have the same carboxylic acid part and similar alcohol part.
  - The key differences are that the target has a methyl group in the para position of the alcohol group, while the analog does not. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicology profiles are expected to be similar.
  - The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - 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.
  - The target and analog show similar alerts for protein binding.
  - 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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