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Short Review

RIFM fragrance ingredient safety assessment, *p*-*t*-butyl-α-methylhydrocinnamic aldehyde, CAS Registry Number 80-54-6

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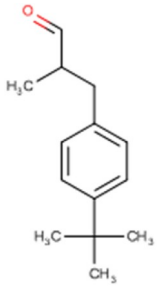

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

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RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

p-t-Butyl-α-methylhydrocinnamic aldehyde was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *p-t*-butyl-α-methylhydrocinnamic aldehyde is not genotoxic. Data on *p-t*-butyl-α-methylhydrocinnamic aldehyde provide a calculated MOE of > 100 for the repeated dose toxicity and developmental and reproductive toxicity endpoints. Data provided *p-t*-butyl-α-methylhydrocinnamic aldehyde a NESIL of 4100 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; *p-t*-butyl-α-methylhydrocinnamic aldehyde is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to *p-t*-butyl-α-methylhydrocinnamic aldehyde is below the TTC (1.-4 mg/day). The environmental endpoints were evaluated; *p-t*-butyl-α-methylhydrocinnamic aldehyde was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2010a; RIFM, 2000a; RIFM, 2000b; ECHA REACH Dossier: 2-(4-tert-Butylbenzyl)propionaldehyde; ECHA, 2011a; SCCS Submission II; SCCS, 2017)
Repeated Dose Toxicity: NOAEL = 4.5 mg/kg/day.	RIFM (2017)
Developmental and Reproductive Toxicity: Developmental Toxicity: NOAEL = 4.1 mg/kg/day. Reproductive Toxicity: NOAEL = 15.1 mg/kg/day.	(RIFM, 2004b; RIFM, 2017)
Skin Sensitization: NESIL = 4100 μg/cm^2.	RIFM (1980a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database; RIFM, 1983b; RIFM, 1980c; RIFM, 1986c)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 96% (OECD 301F)	RIFM (1990b)
Bioaccumulation: Screening-level: 349.8 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: Fish 21-day NOEC: 0.2 mg/L	(ECHA REACH Dossier: 2-(4-*tert*-Butylbenzyl)propionaldehyde; ECHA, 2011a)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish 21-day NOEC: 0.2-mg/L	(ECHA REACH Dossier: 2-(4-*tert*-Butylbenzyl)propionaldehyde; ECHA, 2011a)

RIFM PNEC is: 4 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

1. **Chemical Name:** *p-t*-Butyl-α-methylhydrocinnamic aldehyde
2. **CAS Registry Number**: 80-54-6
3. **Synonyms:** Benzenepropanal, 4-(1,1-dimethylethyl)-.α.-methyl-; BMHCA; *p-t*-Butyl-α-methylhydrocinnamaldehyde; Lilestralis; Lilial; α-Methyl-β-(p-t-butylphenyl)propionaldehyde; *p-t*-Bucinal; 2-(4-*tert*-Butylbenzyl)propionaldehyde; Lysmeral; Butylphenyl methylpropional; p-ｱﾙｷﾙ(C = 3～4)ﾌｪﾆﾙｱﾙｷﾙ(C = 2,3)ｱﾙﾃﾞﾋﾄﾞ; 3-(4-tert-Butylphenyl)-2-methylpropanal; 4-(1,1-Dimethylethyl)-α-methylbenzene propanal; Lysmeral extra; *p-t*-Butyl-α-methylhydrocinnamic aldehyde
4. **Molecular Formula:** $C_{14}H_{20}O$
5. **Molecular Weight**: 204.31
6. **RIFM Number**: 188
7. **Stereochemistry**: α Isomer specified. One stereocenter present and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** (calculated) 280.03 °C (EPI Suite)
2. **Flash Point:** > 100 °C (212 °F) (RIFM, 1990b), > 200 °F; CC (FMA Database), > 100 °C (RIFM Database)
3. **Log K_{OW}:** 4.2 (RIFM, 1994c), 4.36 (EPI Suite)
4. **Melting Point**: (calculated) 46.29 °C (EPI Suite)
5. **Water Solubility:** 0.02% W/V (RIFM, 1990b), 33 mg/L at 20 °C (RIFM, 1995b), 24.3 mg/L at 20 ± 5 °C (RIFM, 1992a), < 10 mg/L at 20 °C (RIFM, 1994b), (calculated) 7.859 mg/L (EPI Suite)
6. **Specific Gravity:** 0.946 g/mL at 20 °C (RIFM, 1994b), 0.942–0.947 @ 20 °C (RIFM Database), 0.9448 (RIFM Database), 0.943 (FMA Database)
7. **Vapor Pressure:** 0.00197 mm Hg @ 20 °C (EPI Suite v4.0), 0.003 mm Hg 20 °C (FMA Database), 0.00358 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless to pale yellow liquid with a powerful, floral-fresh odor

3. Volume of use (worldwide band)

1. > 1000 metric tons per year (IFRA, 2015).

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

1. 95th Percentile Concentration in Hydroalcoholics: 1.4% (RIFM, 2018c)
2. Inhalation Exposure*: 0.0033 mg/kg/day or 0.23 mg/day (RIFM, 2018c)
3. Total Systemic Exposure**: 0.0065 mg/kg/day (RIFM, 2018c)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

1. **Dermal:** 13.5% for hydroalcoholic-based fragrances and deodorant/antiperspirant products; 8.9% for oil-in-water-based products like make-up products, body lotions, hair styling, and bath cleansing products; 10.5% for water-in-oil-based products like face and hand cream products.

Since the Scientific Committee on Consumer Safety (SCCS) Submission II study (described below) follows GLP and OECD TG 428 and accounts for test material penetration and recovery more accurately, dermal absorption for BMHCA was determined using these results instead of those of Hawkins (RIFM, 1994a).

RIFM, 1994a: ^{14}C-BMHCA, *p-t*-butyl-α-methylhydrocinnamic aldehyde, was applied to a 100–cm^2 area on the backs of 3 human volunteers and the applications were occluded with gauze dressings. After 6 h, the dressings were removed, and residual dose material was removed with cotton wool swabs moistened with ethanol. Five successive samples of adhesive "stripping" tape were then applied to 2.5 × 2.5–cm areas of skin and removed. Treated areas of skin were then occluded with fresh gauze dressings until 120 h of application, when they were removed, and 5 similar samples of adhesive "stripping" tape were applied and removed. A mean of 1.4% of applied radioactivity was excreted in urine by the 3 subjects within 24 h. Radioactivity was below the limit of detection in all urine samples collected between 24 h and 120 h after application. Radioactivity was below the limit of detection in feces collected from subjects during hours 0–120 h after application. Radioactivity in plasma samples was below the limit of detection at any time after application, corresponding to concentrations of less than 0.025 μg/mL. A mean 63.12% ± 4.95 standard deviation (SD) of the applied radioactivity was recovered from gauze dressings used to occlude the site of application during hours 0–6, a further mean 3.76% of dose ± 1.95 SD was removed by washing the skin with an ethanol-moistened swab at 6 h, and 3.06% ± 2.77 SD was recovered from gauze dressing used to occlude treated areas of skin during hours 6–120. Results indicate that very little of applied ^{14}C-BMHCA was absorbed through skin into the systemic circulation. While the dermal absorption studies conducted in humans *in vivo* showed that only 1.4% of the applied radioactive dose was absorbed, only 71% of the overall dose was recovered. Based on the presented data combined with the lack of 100% recovery of the test material, an extremely conservative assessment has been taken that approximately 30% of a dermal dose is absorbed.

SCCS Submission II (SCCS, 2017): Dermal absorption of BMHCA has been studied in rats, guinea pigs, and humans *in vitro* and *in vivo*. The BMHCA dermal absorption profile was found to be similar among guinea pigs and humans. In an OECD TG 428/GLP-compliant *in vitro* human skin absorption study, [^{14}C]-BMHCA in ethanol-in-water (1.9%), silicone-in-water (0.1%), water-in-oil (0.1%), and oil-in-water (0.1%) was used to represent a variety of commercial cosmetic formulations. Dermal absorption of BMHCA was assessed by a 2-step experimentation process. Following a single topical (semi-occluded) application on split-thickness human skin membrane mounted on modified Franz-type diffusion cells, absorption was measured 24 h post-dosing as well as 72 h post-dosing. The amounts absorbed at the end of 24 h and 72 h following BMHCA treatment were comparable, suggesting that the extent of absorption does not change over time following a single topical application. After 24 h, 7.52%, 5.1%, 6.3%, and 6.24% of [^{14}C]-BMHCA was absorbed under the test conditions used for hydroalcoholic solution, silicone-in-water, water-in-oil, and oil-in-water formulations, respectively. These experiments were designed to differentiate between extractable (potentially absorbable) and non-extractable (bound, non-absorbable) residues of the test substance; 21%, 27%, 28%, and 38% of the fraction was potentially not absorbable in the respective vehicles. The percentage of systemically-available BMHCA was calculated based on the absorbed dose and subtracting the non-systemically-available fraction from the total applied dose. The systemically-available portion was lower and ranged between 5% and 7% with the highest values obtained for the hydroalcoholic vehicle. However, the treatment material recovery for ethanol-in-water, silicone-in-water, water-in-oil, and oil-in-water were 80%–85%, 83%–89%, 91%–97%, and 88%–96%, respectively. Despite the high recovery, a portion of treatment material still remained unaccounted for. For 2 formulations, 50%–60% of the applied dose was found in the charcoal filter, demonstrating the volatility of BMHCA. Importantly, a decrease in the total recovery was not correlated with a decrease in the percentage of the BMHCA dose absorbed.

The percentage of systemically-available [^{14}C]-BMHCA was calculated by the SCCS as mean +SD, and including the non-absorbable fraction, for water-in-oil and oil-in-water phases to be 10.5% and 8.9%, respectively. However, for the ethanol-in-water and silicone-in-water phases, SCCS used a more conservative approach to calculate the systemically-available percent [^{14}C]-BMHCA by using mean + 2 SD and including the non-absorbable fraction. Hence, the percent [^{14}C]-BMHCA available systemically following ethanol-in-water and silicone-in-water formulations was calculated to be 13.5% and 8.5%, respectively. Considering percutaneous absorption of BMHCA in humans is minimal, dermal absorption of 13.5% was considered for calculating the systemic exposure based on the key *in vitro* study with human skin.

RIFM, 1995a: A comparative oral and dermal absorption study was performed in male rats following GLP with standards comparable to OECD 417 and 427 guidelines. Dermal absorption of [^{14}C]-BMHCA was measured following topical application of the material on shaved backs of the animals. The animals were observed up to 120 h following treatment application. At the end of the observation period, 14.6% (cumulative) of the dose was excreted in the urine, 2% in the feces, and 0.8% was recovered in the cage washings. Overall, approximately 19% of the applied dose was found in excreta and tissues, representative of the extent of absorption. However, there are no data on amount of treatment material recovered following topical application.

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

6. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs 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

7. Metabolism

RIFM, 2010b: A study was conducted to investigate the *in vitro* metabolism of *p-t*-butyl-α-methylhydrocinnamic aldehyde (^{14}C-BMHCA) in rats, mice, rabbits, and humans. Liver microsomes and hepatocytes of males were used. Liver microsomes and hepatocytes were incubated in triplicates based on a standardized amount of protein/cell numbers with ^{14}C-BMHCA at nominal substrate concentrations of 10, 50, and 100 μM. Incubations with microsomes were carried out

with 0.5 mg microsomal protein/mL incubate. Metabolic profiles were detected and quantified by radio-HPLC after appropriate work-up procedures of received incubates. For most hepatocyte incubations with BMHCA, the corresponding carboxylic acid (lysmerylic acid) was the largest component. Other main components were (E)-3-(4-tert-butylphenyl)-2-methyl-acrylic acid and 4 glucuronic acid conjugates of metabolites. *p-tert*-Butylbenzoic acid (TBBA) was observed at the highest levels in rats; the levels observed in humans were found to be approximately 4-fold lower than in rat hepatocytes and were comparable to plasma concentrations found in the rabbits at toxicologically-relevant doses, a species not sensitive to BMHCA-induced testicular toxicity. TBBA was conjugated with glycine to form *p-tert*-butyl-hippuric-acid (TBHA) in rats and mice but not in rabbits or humans. However, the amounts of TBHA in rat hepatocyte cultures were surprisingly low.

In rat hepatocytes, BMHCA and TBBA are rapidly transformed to TBBA-CoA followed by accumulation of the glycine conjugate, a phenomenon not seen in human hepatocytes (CLH Report; ECHA, 2017). In addition, *in vitro* and *in vivo* studies highlight the species-specific differences in BMHCA metabolism leading to reproductive toxicity. *In vitro* studies demonstrate that the formation of TBBA in human hepatocytes is significantly lower in comparison to rats.

RIFM, 1985: Oral 5-day toxicity studies were conducted with BMHCA on mice, rats, guinea pigs, dogs, and monkeys. Twenty-four-hour urine samples were collected after the last application of the compound and analyzed for the 2 expected metabolites TBBA and TBHA by GC and in some cases GC-MS. In male mice, the dose level was 100 mg/kg *t*-Butylbenzoic acid (TBBA) was found in very low concentrations (< 0.8% of the applied dose) in urine samples of BMHCA-treated mice. TBHA was found at much higher concentrations (14.5% of the applied dose) in urine samples of mice treated with BMHCA. In male rats, dose levels were 50, 100, 200, and 400 mg/kg. TBBA (7–19%) was found in urine samples of BMHCA-treated rats. TBHA was found in very low concentrations (up to 1%) in urine samples of rats treated with BMHCA. In male guinea pigs, the dose level was 100 mg/kg. TBBA was found in very low concentrations in urine samples of BMHCA-treated guinea pigs. Much higher concentrations of TBHA were found in urine samples of guinea pigs treated with BMHCA. In male and female dogs, the dose level was 50 mg/kg. In BMHCA-treated dogs, TBBA levels were 3–4% of the applied dose in urine samples, and TBHA was found in lower concentrations (1%). In male monkeys, the dose level was 100 mg/kg. TBBA levels were 3–11% in urine samples of BMHCA-treated monkeys. TBHA was found in very low concentrations (< 0.1%) in urine samples of monkeys treated with BMHCA. Compared to TBHA, TBBA was found as the predominant urinary metabolite of rats, dogs, and monkeys. TBHA levels predominated in mice and guinea pigs. (see Fig. 1)

8. Natural occurence (discrete chemical) or composition (NCS)

p-t-Butyl-α-methylhydrocinnamic aldehyde is not reported to occur in foods 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 05/21/19 (ECHA, 2011a).

10. Conclusion: The maximum acceptable concentrations[a] in finished products for *p-t*-butyl-α-methylhydrocinnamic aldehyde are detailed below

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.0
2	Products applied to the axillae	0.090
3	Products applied to the face/body using fingertips	0.040
4	Products related to fine fragrances	1.4
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.060
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.050
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.050
5D	Baby cream, oil, talc	0.017
6	Products with oral and lip exposure	0.0
7	Products applied to the hair with some hand contact	0.040
8	Products with significant ano-genital exposure (tampon)	0.017
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.10
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.10
10B	Aerosol air freshener	0.63
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.017
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	16

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For p-t-butyl-α-methylhydrocinnamic aldehyde, the basis was the reference dose of 0.041 mg/kg/day, a skin absorption value of 14%, and a skin sensitization NESIL of 4100 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, *p-t*-butyl-α-methylhydrocinnamic aldehyde (BMHCA) does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of BMHCA has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with BMHCA in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 in *Salmonella typhimurium* strains TA98, TA100, TA1537, and *Escherichia coli* strain WP2uvrA (SCCS, 2017). However, an increase in the number of revertant colonies was observed for TA1535 in the first experiment

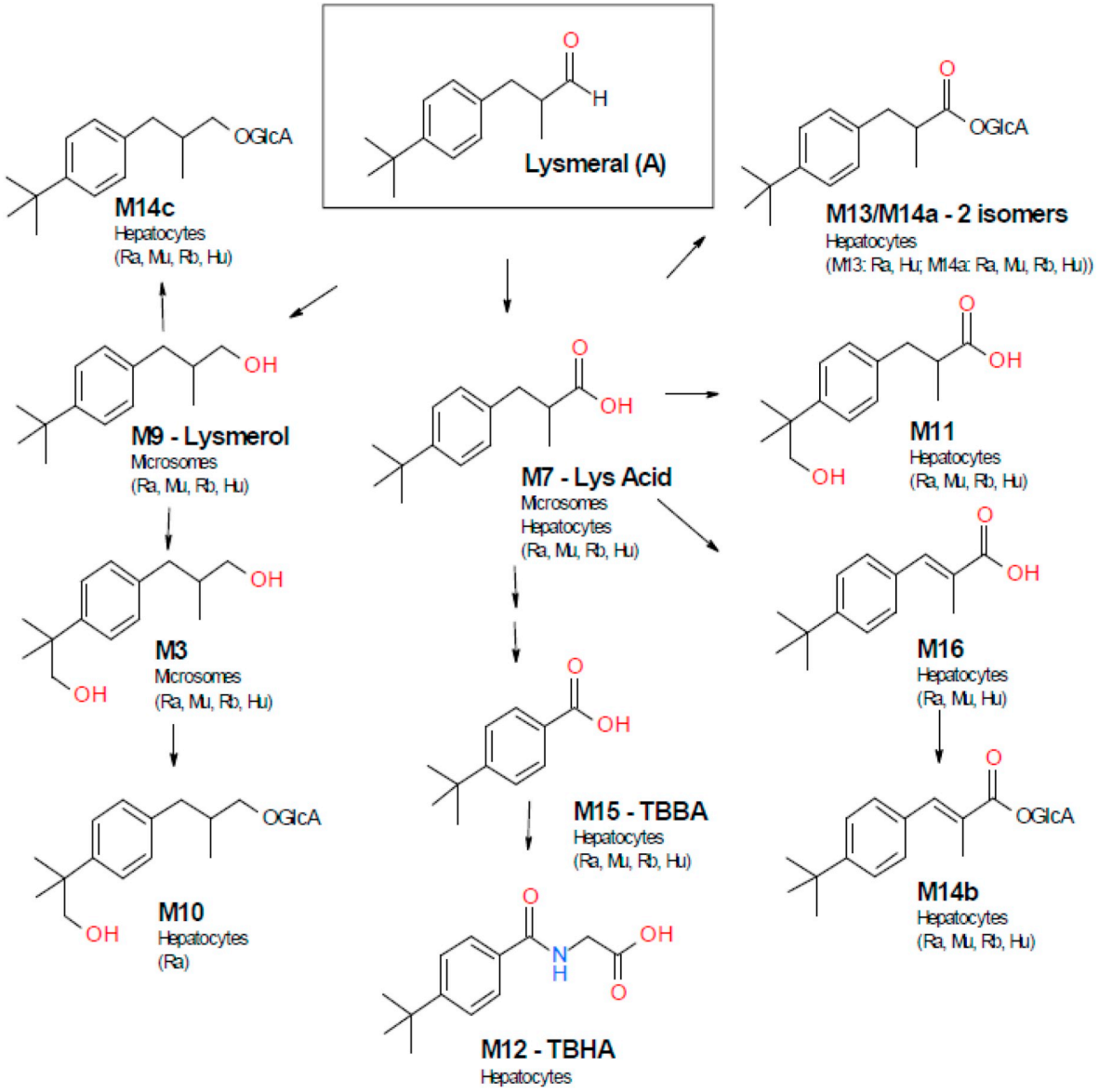

Fig. 1. Schematic representation of BMHCA (Lysmeral) metabolism in liver microsomes and hepatocytes. (Ra = rat; Mu = mouse; Rb = rabbit; Hu = humans).

(plate incorporation method) but not in the follow-up preincubation test. The increase observed consisted of an isolated statistically significant increase in colony frequency at non-bacteriotoxic concentrations noted in 1 single concentration (150 μg/plate) in the presence of S9. This finding was also not reproducible in a confirmatory plate incorporation test conducted in the presence of S9. At higher concentrations of the test material, a concentration-dependent increase of colony numbers associated with a sparse bacterial background lawn was noted for TA1535. This colony number increase has been suggested by the authors to result from residual histidine levels available to a small number of surviving His-bacteria in the presence of bacteriotoxic BMHCA concentrations (although likely, this has not been confirmed experimentally). Under the conditions of the study, the authors considered BMHCA to be equivocal in the Ames test. In another study, the mutagenic activity of BMHCA was evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* WP2uvrA were treated with BMHCA in DMSO at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2011a). Under the conditions of the study, BMHCA was not mutagenic in the Ames test. Along with this study, 3 separate Ames assays have been conducted, which also resulted in an overall negative outcome (RIFM, 1984c; Disotto, 2014; RIFM, 2018a). Sporadic but no relevant increases in the mean number of revertant colonies were reported for the *Salmonella* strain TA1538 (without metabolic activation only) (RIFM, 1984c).

The overall picture of several bacterial reverse mutation assays performed over more than 3 decades is mostly consistent. The majority of mutagenicity data in bacteria provide no evidence for the mutagenic potential of BMHCA. The equivocal findings reported in 1 of the Ames tests for *Salmonella* strain TA1535 result from a study insufficient in terms of procedure and reporting; this observation was not confirmed in the respective preincubation test, and no corresponding increases of other strains (e.g., TA100) were observed (Roche, 1984, in SCCS, 2017). Findings in the *Salmonella* strain TA1538 were not reproducible in further trials, followed no concentration response, and the study is considered to have limited validity since spontaneous revertant

frequencies were unusually low. The lack of biological relevance of this variation is confirmed by the results in TA98. When investigating the same type of mutagenic lesions in this tester strain, no effects/variations were observed.

A mammalian cell gene mutation assay was conducted according to OECD TG 476/GLP guidelines. Chinese hamster lung cells (V79) were treated with BMHCA in DMSO at concentrations of 128 μg/mL (as determined in a preliminary toxicity assay) for 4 and 24 h. Effects were evaluated both with and without metabolic activation. No statistically significant/biologically relevant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (RIFM, 2010a). Under the conditions of the study, BMHCA was not mutagenic to mammalian cells *in vitro*. Additionally, in an *in vitro* comet study using human colonic epithelial cells (HCEC), a negative outcome was observed (Disotto, 2014).

A mammalian cell gene mutation assay (mouse lymphoma assay) was conducted according to OECD TG 476/GLP guidelines. An L5178Y mouse lymphoma cell line was treated with BMHCA in DMSO at concentrations up to 72 μg/mL and 70 μg/mL (as determined in a preliminary toxicity assay) for 4 and 24 h, respectively. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (SCCS, 2017). Under the conditions of the study, BMHCA was not mutagenic to mammalian cells *in vitro*.

Taken together, 2 different mutagenicity studies in mammalian cells investigating the same mutagenic endpoint (gene mutation at both the HPRT- and the tk ± locus) supported the absence of the mutagenic potential of BMHCA. Although methodological shortcomings exist, the highly sensitive indicator test for DNA damage, the comet assay in human colonic epithelial cells, reported in the literature, adds further evidence for an absence of DNA-damaging potential of BMHCA. Thus, the negative result generated in mammalian cells as well as the absence of an effect in the comet assay support the weight of evidence that BMHCA is non-genotoxic *in vitro*.

The clastogenicity of BMHCA was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations. Chinese hamster ovary cells were treated with BMHCA in DMSO at concentrations up to 2040 μg/mL in the presence and absence of metabolic activation. Significant increases in the frequency of cells with structural chromosomal aberrations were observed only in the 4-h treatment group without S9 (RIFM, 2000a). Under the conditions of the study, it was concluded that BMHCA was positive for the induction of chromosome aberrations in the absence of S9 activation, but it was negative with S9 (RIFM, 2000a). The clastogenic activity of BMHCA was also evaluated in an *in vitro* micronucleus test using human peripheral blood lymphocytes in DMSO at concentrations up to 500 μM in the absence of metabolic activation (S9). BMHCA did not induce binucleated cells with micronuclei (Disotto, 2014). Furthermore, an additional *in vitro* micronucleus test was conducted in compliance with GLP regulations and in accordance with OECD TG 487, which also resulted in a negative outcome (RIFM, 2018b). Under the conditions of the study, BMHCA was considered to be non-clastogenic in the *in vitro* micronucleus test. The clastogenic activity of BMHCA was also evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD. The test material was administered in corn oil via intraperitoneal injection to groups of male and female IRC mice. Doses of 150, 300, or 600 mg/kg were administered. Mice from each dose level were euthanized at 24 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a biologically-relevant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2000b). Under the conditions of the study, BMHCA was considered to be not clastogenic in the *in vivo* micronucleus test. This data indicates that the positive effects observed in the *in vitro* chromosome aberration assay without metabolic activation do not have relevance in the *in vivo* model (RIFM, 2000b). Taken together and based on the data available, BMHCA does not present a concern for genotoxic potential.

Additional references: RIFM, 1999b; RIFM, 2001a.

Literature search and risk assessment completed on: 07/13/18.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for BMHCA is adequate for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on BMHCA that can be used to support the repeated dose toxicity endpoint.

Based on the previous SCCS Opinions (Submission I; SCCS, 2016), the toxicity of BMHCA after repeated oral application was investigated in several animal species. Decreases in body weights and food consumption and/or clinical signs of toxicity were observed after subchronic oral administration of BMHCA at doses of ≥50 mg/kg/day (rats) and ≥200 mg/kg/day (dogs). In oral studies, rats were found to be more sensitive than dogs to this compound irrespective of the length of treatment. Clinical chemistry and histopathological examinations repeatedly revealed adverse effects on the liver and male reproductive system (testicular toxicity). An OECD 408/GLP oral gavage 90-day subchronic study was conducted with FU SPF albino rats. Groups of 14 rats/sex/dose were administered BMHCA via oral gavage at doses of 0, 2, 5, 25, or 50 mg/kg/day in rape oil, once each day, 5 days per week, for 13 consecutive weeks. An additional group of 28 animals were administered 50 mg/kg/day, with continued observations during a period of 4 weeks after the treatment. Eight controls (4 rats/sex) were also observed during a 4-week follow-up period. BMHCA-induced systemic toxicity (decreases in plasma cholinesterase levels) was observed in both sexes at doses ≥25 mg/kg/day. Furthermore, effects on adrenal glands in females were also observed at doses ≥25 mg/kg/day. The NOAEL for systemic toxicity was considered to be 5 mg/kg/day (RIFM, 1986a; RIFM, 1991a; and SCCS, 2016).

An OECD 443/GLP modified extended 1-generation reproduction study was conducted in Wistar rats. Groups of rats were administered the test material BMHCA (microcapsules) in the diet at nominal doses of 0, 1, 3, and 10 mg/kg/day (equivalent to an overall actual dose of 0, 1.4, 4.5, or 15.1 mg/kg/day). The control, low-, and mid-dose groups consisted of 35 rats/sex, while the high-dose group consisted of 40 rats/sex. An additional placebo control group (35 rats/sex) was dosed with placebo alginate (encapsulated) without BMHCA. Parental animals were dosed for approximately 2 weeks prior to mating, through mating (up to 2 weeks), and for a maximum of 6 post-mating weeks (males) or gestation (3 weeks) and lactation (3 weeks) for females. The NOAEL for the systemic toxicity of BMHCA was established to be a nominal dose of 3 mg/kg/day or the actual dose of 4.5 mg/kg/day for the F0 and F1 parental as well as adolescent animals, based on distinct liver toxicity and corresponding effects on food consumption, body weights, and clinical-pathological parameters (predominantly in females) (RIFM, 2017; also available at SCCS, 2017).

The most conservative NOAEL of 4.5 mg/kg/day from the OECD 443 study was selected for the repeated dose toxicity endpoint.

Therefore, the BMHCA MOE for the repeated dose toxicity endpoint can be calculated by dividing the BMHCA NOAEL in mg/kg/day by the total systemic exposure to BMHCA, 4.5/0.0065 or 692.

When correcting for skin absorption (see Section V), the total systemic exposure to BMHCA (6.5 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional references: RIFM, 2006b; RIFM, 2002b; RIFM, 1995a; Charles, (2009); ECHA, 2011b; ECB, 2000; ECHA RAC, 2011; Hoechst-Celanese, (1988); Procter and Gamble company, 1986; Darmer, (1984);

Shell, (1982); Hunter, (1965); BASF, 1986, Lu, (1984); Lu, (1987); Nishihara, (2000); RIFM, 2006c; RIFM, 1984b; RIFM, 1986a; RIFM, 1987a; RIFM, 1982b; RIFM, 1987b; RIFM, 1994d; RIFM, 1985; RIFM, 1982c; RIFM, 1982d; RIFM, 1986b; RIFM, 1982e; RIFM, 2010b; RIFM, 1982h; Scherer, (2017); RIFM, 1991b; US EPA, 1991, RIFM, 1984a; RIFM, 2008d; US EPA, 1982b; US EPA, 1983; BASF, 1986; US EPA, 1981; US EPA, 1982f; US EPA, 1975a.

Literature search and risk assessment completed on: 10/08/18.

11.1.3. Developmental and reproductive toxicity

The MOE for BMHCA is adequate for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on BMHCA that can be used to support the developmental and reproductive toxicity endpoints.

An OECD 414 oral gavage prenatal developmental toxicity study conducted in pregnant female Wistar rats. Groups of 25 rats/dose were administered test material BMHCA via oral gavage at nominal doses of 0, 5, 15, or 45 mg/kg/day (effective dose of 0, 4.1, 12.7, or 40.7 mg/kg/day, respectively) in olive oil on days 6–20 post coitum (p.c.). At 45 mg/kg/day, dams exhibited statistically significant increased resorption rates (post-implantation loss 15.1%), a lower number of live fetuses/dam (7.4 vs 8.1 in the controls), statistically significant lower mean fetal body weights (about 19% below controls), and a statistically significant increased rate of fetuses/litter with skeletal variations (delays/minor disturbances in ossification, predominantly of skull, vertebrae and sternebrae, supernumerary 14th ribs). At 15 mg/kg/day, statistically significant lower mean fetal body weights (about 8% below controls) and a statistically significant increased rate of fetuses/litter with skeletal variations (delays/minor disturbances in ossification, predominantly of vertebrae and sternebrae, supernumerary 14th ribs) were reported. Clear signs of maternal toxicity, which included reduced food consumption, impaired body weights, and alterations in clinical chemistry accompanied by liver weight changes were observed among mid- and high-dose dams. The NOAEL for maternal and prenatal developmental toxicity was considered to be 5 mg/kg/day or the effective dose of 4.1 mg/kg/day, based on reduced fetal body weight and increased incidences of skeletal variation of the fetuses among higher dose group dams (RIFM, 2004b).

In an OECD 443/GLP modified extended 1-generation reproduction toxicity study, the NOAEL for systemic toxicity of BMHCA applied in encapsulated form at 0, 1, 3, or 10 mg/kg/day (equivalent to an overall mean dose of 0, 1.4, 4.5, or 15.1 mg/kg/day) was established at 3 mg/kg/day or the mean dose of 4.5 mg/kg/day for the F0 and F1 parental as well as adolescent animals, based on distinct liver toxicity and corresponding effects on food consumption, body weights, and clinical-pathological parameters (predominantly in females). The NOAEL for reproductive toxicity of BMHCA in this study was established at 10 mg/kg/day or the mean dose of 15.1 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity in the F1 and F2 progeny was 3 mg/kg/day or the mean dose of 4.5 mg/kg/day, based on reduced pup body weights in the F1 and F2 offspring of the highest dose group. As these weight reductions were only observed in the presence of maternal toxicity, including lower weight gain during pregnancy, they are not considered as an indication for specific developmental toxicity. In addition, the effect represented a reversible, transient, and isolated reduction of AChE activities in serum, erythrocytes, and diaphragm tissue, and affected functional parameters or clinical signs corresponding to developmental neurotoxicity were not observed. In adult animals, BMHCA has repeatedly been identified to decrease serum and erythrocyte (but no brain) cholinesterase activities, and this effect has not been associated with any adverse outcome in these studies. Thus, based on the absence of adverse clinical or pathological consequences, the transient and isolated effect on AChE in the offspring is not considered sufficient to lower the NOAEL for developmental neurotoxicity. (RIFM, 2017; SCCS, 2017).

The most conservative NOAEL of 4.1 mg/kg/day from the OECD 414 study was selected for the developmental toxicity endpoint. **Therefore, the BMHCA MOE for the developmental toxicity endpoint can be calculated by dividing the BMHCA NOAEL in mg/kg/day by the total systemic exposure to BMHCA, 4.1/0.0065 or 631.**

Based on the SCCS Opinions (Submission I; SCCS, 2016; Submission II; SCCS, 2017), adverse effects of BMHCA on the male reproductive system have been consistently observed in several repeated dose and reproduction toxicity studies. A NOAEL of 25 mg/kg/day in male rats is substantiated by studies applying the test material for 5 days, 90 days, or in the 1-generation range finding study, over 6 weeks prior to mating. In all the studies available, testicular toxicity in rats was accompanied by signs of systemic toxicity. By contrast, other species such as dogs were less sensitive. In dogs, a NOAEL of 40 mg/kg/day has been established, based on the onset of testicular toxicity after treatment periods of 2 weeks and 3 months. No evidence for testicular toxicity was observed in mice, guinea pigs, rabbits, and rhesus monkeys. Therefore, male rats were the most sensitive species with regard to BMHCA-mediated testicular toxicity.

Species specificity for BMHCA-induced testicular toxicity is reflected by species-dependent differences in the conversion of BMHCA to TBBA in hepatocytes. Toxicokinetic studies revealed that hepatic metabolism of BMHCA in rats results in significantly higher levels of TBBA when compared to other species. TBBA levels in human hepatocytes were approximately 4-fold lower than rats at corresponding concentrations and were comparable to TBBA levels in the rabbit, a species not sensitive to testicular toxicity. BMHCA, *p-tert*-benzaldehyde (TBB), *p-tert*-butyltoluene (TBT), and the shared metabolite TBBA, all share a similar testes toxicity profile, in which the formation of TBBA-CoA conjugates represent a key metabolic event for BMHCA-induced testicular toxicity. A strong correlation has been established between the formation of TBBA-CoA conjugates in rat hepatocytes, disruption of lipid synthesis, and testicular toxicity. Short-term studies on TBBA, TBT, and TBB have been conducted in rats via the oral route. Results suggest that TBBA, TBT, and TBB all exert testicular toxicity, along with systemic toxicity, since TBB and TBT will metabolize into TBBA and subsequently form TBBA-CoA conjugates. Taken altogether, the low magnitude of TBBA formation in human hepatocytes along with rapid decreases of TBBA-CoA conjugates in human hepatocytes indicate that testicular toxicity is a species-specific effect with little relevance to humans (ECHA, 2017; SCCS, 2017).

Though human relevance is unlikely, the most conservative reproductive toxicity NOAEL of 15.1 mg/kg/day from the OECD 443 rat study was selected for the reproductive toxicity endpoint, since testicular and sperm toxicity were the key reproductive toxicity effects of BMHCA and were observed at doses above 25 mg/kg/day. **Therefore, the BMHCA MOE for the reproductive toxicity endpoint can be calculated by dividing the BMHCA NOAEL in mg/kg/day by the total systemic exposure to BMHCA, 15.1/0.0065 or 2323.**

When correcting for skin absorption (see Section V), the total systemic exposure to BMHCA (6.5 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental and reproductive toxicity endpoints at the current level of use.

Section X provides the maximum acceptable concentrations in

finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008a; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose (RfD) of 0.041 mg/kg/day.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for BMHCA was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 4.1 mg/kg/day by the uncertainty factor, 100 = 0.041 mg/kg/day.

Additional references: RIFM, 2006c; RIFM, 2002b; RIFM, 1991b; US EPA, 1991; RIFM, 1982a; RIFM, 1983a; RIFM, 1984a; RIFM, 2008d; RIFM, 1982d; RIFM, 1986b; RIFM, 1982e; RIFM, 1995a; RIFM, 2006b; RIFM, 1985; RIFM, 1982c; US EPA, 1982a; RIFM, 1982h; RIFM, 1987a; RIFM, 1982b; RIFM, 1987b; RIFM, 1984b; RIFM, 2008b; RIFM, 2008c; RIFM, 1994d; RIFM, 2011; RIFM, 2009; Charles, (2009); ECB, 2000; Hoechst-Celanese, (1988); US EPA, 1982b; US EPA, 1983; Procter and Gamble company, 1986; US EPA, 1982c; US EPA, 1986; Darmer, (1984); US EPA, 1982d; Shell, (1982); Hunter, (1965); US EPA, 1982e; BASF, 1986; US EPA, 1981; US EPA, 1982f; Lu, (1984); US EPA, 1975b; US EPA, 1975a; Lu, (1987); Nishihara, (2000); ECHA 2011 (accessed 08/01/18).

Literature search and risk assessment completed on: 09/19/18.

11.1.4. Skin sensitization

Based on the available data, BMHCA is considered to be a skin sensitizer with a defined NESIL of 4100 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, BMHCA is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree 2.6.13; OECD Toolbox v4.1). BMHCA was found to be positive in an *in chemico* direct peptide reactivity assay (DPRA), *in vitro* human cell line activation test (h-CLAT), and U937-CD86 test; however, it was negative in the *in vitro* KeratinoSens assay (Natsch, 2013; Gerberick, 2004; Nukada, 2011; Piroird, 2015). In 7 murine local lymph node assays (LLNAs), BMHCA was found to be sensitizing with a weighed mean EC3 value of 2454 μg/cm^2 (RIFM, 2001b; RIFM, 2001c; RIFM, 2001d; RIFM, 2001e; RIFM, 2001f; Basketter, 2001; Gerberick, 2005; RIFM, 2001g). In guinea pigs, a maximization test, a Freund's complete adjuvant test, a sensitization by KAO test procedure, and a Buehler test with BMHCA presented reactions indicative of sensitization (RIFM, 1988a; RIFM, 1982f; RIFM, 1982g; RIFM, 1979). However, in 2 other guinea pig maximization tests, BMHCA did not present reactions indicative of sensitization (RIFM, 1990a; RIFM, 1980b). In a human maximization test, no skin sensitization reactions were observed when tested at 4% (2760 μg/cm^2) (RIFM, 1972a). However, in another human maximization test, BMHCA showed sensitization reactions when tested at 5% (3450 μg/cm^2) (RIFM, 1971a); this may have been due to spillover from phenylacetaldehyde. In a confirmatory human repeat insult patch test (HRIPT) with 25% (29535 μg/cm^2) of BMHCA in 3:1 ethanol:diethyl phthalate (EtOH:DEP), reactions indicative of sensitization were observed in 1/119 volunteers (RIFM, 1999a). However, in 3 other HRIPTs, BMHCA did not present reactions indicative of sensitization when tested at 25% (29528 μg/cm^2 in 1:3 EtOH:DEP), 5.5% (4125 μg/cm^2 in alcohol SDA 39C), and 5% (7500 μg/cm^2 in DEP) in 106, 64, and 103 volunteers, respectively (RIFM, 2002a; RIFM, 1980a; RIFM, 1989a). The NESIL of 4100 μg/cm^2 was derived from the RIFM, 1980a study (RIFM, 1980a) as it is more conservative and utilizes an ethanol vehicle (Politano, 2008).

Based on weight of evidence from structural analysis and animal and human studies, BMHCA is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 4100 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008a; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.041 mg/kg/day.

Additional references: Klecak, (1985); Natsch, (2007); McKim, (2010); Isola, (2001); Basketter, (2003); Lalko, (2004); Patlewicz, (2003); RIFM, 1988b; Ishihara, (1986); RIFM, 1986a; RIFM, 1980b; RIFM, 2004a; RIFM, 2005a; RIFM, 2001h; RIFM, 2003; RIFM, 2005b; RIFM, 2006a; US EPA, 1980; RIFM, 1957; Cocchiara, (2003); RIFM, 1975; RIFM, 1965; RIFM, 1971b; RIFM, 1972b; RIFM, 1964; ECHA, 2011a (accessed 04/12/18); SCCS, 2016.

Literature search and risk assessment completed on: 04/19/18.

11.1.5. Phototoxicity/photoallergenicity

Based on UV spectra and available study data, BMHCA does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity. Phototoxicity and photoallergenicity were assessed in guinea pigs with solutions of 3% and 10% BMHCA, and no reactions were seen (RIFM, 1983b; RIFM, 1986c; RIFM, 1980c). Based on the lack of significant absorbance in the critical range and the absence of reactions in guinea pig phototoxicity and photoallergenicity studies, BMHCA does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for BMHCA were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry, 2009).

Additional references: None.

Literature search and risk assessment completed on: 04/11/18.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for BMHCA is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on BMHCA. Based on the Creme RIFM Model, the inhalation exposure is 0.23 mg/day. This exposure is 6.1 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional references: None.

Literature search and risk assessment completed on: 03/07/19.

Table 1
Data Summary for *p*-*t*-butyl-α-methylhydrocinnamic aldehyde.

LLNA Weighted Mean EC3 Value μg/cm[b] (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (Induction) μg/cm[b]	NOEL-HMT (Induction) μg/cm[b]	LOEL[b] (Induction) μg/cm[b]	WoE NESIL[c] μg/cm[b]
2454 [7]	Weak	4125	2760	29528	4100

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of BMHCA was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework BMHCA 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 EPI Suite v4.11 (US EPA, 2012a) identified BMHCA as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), BMHCA presents a risk to the aquatic compartment in the risk screening assessment.

11.2.2.1. Key Studies**Biodegradation:**

RIFM, 1996: A study was conducted following OECD 301B guidelines. Ten mg/L of the test material was incubated for 28 days. At the end of 28 days, −4.5% biodegradation was observed.

RIFM, 1993a: A study was conducted following OECD 301B guidelines. Ten mg/L of the test material was incubated for 56 days. At the end of 56 days, 66.8% biodegradation was observed.

RIFM, 1990b: A study was conducted following Method F in the Assessment of Biodegradability (Blue Book series). The test concentration was equivalent to 50.04 mg/L dissolved organic carbon. The test duration was 31 days. At the end of the study, biodegradation was 96.0%

RIFM, 1994b: A study was conducted following an OECD 301F Guideline (Modified MITI – Test I procedure). The incubation period was 28 days. At the end of the study, 68% biodegradation was observed at 100 mg/L, and 84% biodegradation was observed at 50 mg/L.

RIFM, 1992b: A study was conducted following an OECD 301F Guideline. The test concentration was 100 mg/L, and the test duration was 28 days. At the end of the study, less than 20% biodegradation was observed.

Ecotoxicity:

RIFM, 1989b: An algae growth inhibition study was conducted following Method DIN 38412 L9 (Inhibition of cell proliferation by algae). At the end of 72 h, the E_yC50 was 74.8 mg/L (95.3 mg/L at 96 h). The E_bC50 at 72 h was 28.2 mg/L (18.8 mg/L at 96 h). The NOEC was < 2.5 mg/L (72 and 96 h).

RIFM, 1988c: Two *Daphnia* immobilization studies were reported. In the first study, following OECD 202 guidelines, the EC50 was reported as 10.7 mg/L at the end of the study at 48 h (RIFM, 1993b). In a second study, following method ISO 6341 (DIN 38412), the EC50 value was determined to be 2.51 mg/L at 48 h.

RIFM, 2004c: A fish (*Brachydanio rerio*) acute toxicity study was conducted according to the OECD 203 guidelines under a flow-through system. The reported 96-h LC50 was 2.04 mg/L, based on the mean of analytically determined concentrations and 2.65 mg/L based upon the analytically determined concentrations plus its oxidation product, the corresponding acid.

Other available data:

BMHCA has been registered under REACH and the following additional data is available:

An algae growth inhibition study was conducted following OECD 201 TG. The reported 72-h E_bC50 was 16.5 mg/L, the EyC50 was 32.5 mg/L, and the NOEC (biomass) was 8.6 mg/L.

A *Daphnia magna* immobilization study was conducted following OECD 202 guidelines. The 48-h EC50 was reported as 9.84 mg/L.

A fish (*Pimaphales promelas*) short-term reproduction study was conducted according to the OECD 229 Guidelines under flow-through conditions. The overall 21-day NOEC was reported to be greater than 0.2 mg/L (ECHA, 2011a).

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	3.36			1000000	0.00336	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.823	0.444	1.114	10000	0.0444	Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.775	1.235	2.130			Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	2.04		0.2	50	4.0	
Daphnia		2.51				
Algae		28.8	<2.5			

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	4.2	4.2
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	> 1000	> 1000
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

The RQs for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 4.0 μg/L. The revised PEC/PNECs for North America and Europe are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature search and risk assessment completed on: 03/13/19.

12. Literature search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

12.1. Search keywords: CAS number and/or material names

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/21/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives

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