Food and Chemical Toxicology 141 (2020) 111425

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, 3-(*p-tert*-butylphenyl)-2-methylpropanol (Lysmerol), CAS Registry Number 56107-04-1

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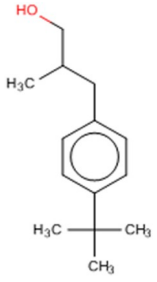
Version: 100818. This version replaces any previous versions.
Name: 3-(*p-tert*-Butylphenyl)-2-methylpropanol CAS Registry Number: 56107-04-1



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
EU - Europe/European Union
GLP - Good Laboratory Practice

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https://doi.org/10.1016/j.fct.2020.111425
Received 17 September 2019; Received in revised form 8 April 2020; Accepted 7 May 2020
Available online 24 May 2020

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
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
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.

3-(*p-tert*-Butylphenyl)-2-methylpropanol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog *p-t*-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6) show that 3-(*p-tert*-butylphenyl)-2-methylpropanol is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to 3-(*p-tert*-butylphenyl)-2-methylpropanol is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog 2-(4-methylphenoxy)ethanol (CAS # 15149-10-7) show that there are no safety concerns for 3-(*p-tert*-butylphenyl)-2-methylpropanol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 3-(*p-tert*-butylphenyl)-2-methylpropanol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-(*p-tert*-butylphenyl)-2-methylpropanol was found not to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2010; RIFM, 2000a; RIFM, 2000b; ECHA Dossier: 2-(4-tert-butylbenzyl)propionaldehyde [ECHA, 2011a]; SCCS Submission II [SCCS, 2017])

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.

Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: No safety concerns under the current, declared levels of use. (RIFM, 2002; RIFM, 1971; RIFM, 1972)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Screening-level: 80.7% (OECD 301B)

(ECHA REACH Dossier: 3-(p-tert-butylphenyl)-2-methylpropanol [ECHA, 2011b])

Bioaccumulation:

Screening-level: 201.6 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC_{50}: 2.365 mg/L (RIFM Framework; Salvito, 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito, 2002)

Critical Ecotoxicity Endpoint: Fish LC_{50}: 2.365 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.002365 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 3-(*p-tert*-Butylphenyl)-2-methylpropanol
2. **CAS Registry Number:** 56107-04-1
3. **Synonyms:** Benzenepropanol, 4-(1,1-dimethylethyl)-β-methyl-; 3-(4-*tert*-Butylphenyl)-2-methylpropan-1-ol; Lysmerol; 3-(*p-tert*-Butylphenyl)-2-methylpropanol
4. **Molecular Formula:** $C_{14}H_{22}O$
5. **Molecular Weight:** 206.32
6. **RIFM Number:** 5743
7. **Stereochemistry:** Isomer not specified. One chiral center and 2 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 298.56 °C (EPI Suite)
2. **Flash Point:** 115 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.38 (EPI Suite)
4. **Melting Point**: 61.11 °C (EPI Suite)
5. **Water Solubility:** 23.65 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000329 mm Hg @ 20 °C (EPI Suite v4.0), 6.82e-005 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark of concern (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not available

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Deodorant Spray:** 0.24% (RIFM, 2016)

No reported use in hydroalcoholics

3. **Inhalation Exposure*:** 0.00016 mg/kg/day or 0.012 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0091 mg/kg/day (RIFM, 2016)

*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 IV. 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).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. **Analogs** Selected:
   a. **Genotoxicity:** *p-t*-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-(4-methylphenoxy)ethanol (CAS # 15149-10-7)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

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

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

3-(*p-tert*-Butylphenyl)-2-methylpropanol is not 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. Reach dossier

Available; accessed 12/12/18.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 3-(*p-tert*-Butylphenyl)-2-methylpropanol does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 3-(*p-tert*-Butylphenyl)-2-methylpropanol was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: < 80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic or clastogenic activity of 3-(*p-tert*-Butylphenyl)-2-methylpropanol; however, read-across can be made to *p-t*-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6; see Section V).

The mutagenic activity of *p-t*-butyl-α-methylhydrocinnamic aldehyde 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/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with *p-t*-butyl-α-methylhydrocinnamic aldehyde 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 TA98, TA100, TA1537, and *Escherichia coli* strain WP2uvrA (SCCS Submission II; SCCS, 2017). However, an increase in the number of revertant colonies was observed for TA 1535 in the first experiment (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 test item concentrations, a concentration-dependent increase of colony numbers associated with a sparse bacterial background lawn was noted for TA 1535. 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 *p-t*-butyl-α-methylhydrocinnamic aldehyde to be equivocal in the Ames test. In another study, the mutagenic activity of *p-t*-butyl-α-methylhydrocinnamic aldehyde 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 *p-t*-butyl-α-methylhydrocinnamic aldehyde 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, *p-t*-butyl-α-methylhydrocinnamic aldehyde was not mutagenic in the Ames test. Along with this study, 2 separate Ames assays have been conducted, which also resulted in an overall negative outcome (RIFM, 1984; Disotto, 2014). Sporadic but no relevant increases in the mean number of revertant colonies were reported for the *Salmonella* strain TA1538 (without metabolic activation only) (RIFM, 1984).

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 a mutagenic potential of BMHCA. The equivocal findings reported in one 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 (i.e. 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. In this tester strain, investigating the same type of mutagenic lesions, 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 *p-t*-butyl-α-methylhydrocinnamic aldehyde 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 item, either with or without metabolic activation (RIFM, 2010). Under the conditions of the study, *p-t*-butyl-α-methylhydrocinnamic aldehyde 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 item, 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 a 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 a DNA damaging potential of BMHCA. 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 *p-t*-butyl-α-methylhydrocinnamic aldehyde was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations. Chinese hamster ovary cells were treated with *p-t*-butyl-α-methylhydrocinnamic aldehyde 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 *p-t*-butyl-α-methylhydrocinnamic aldehyde 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 *p-t*-butyl-α-methylhydrocinnamic aldehyde 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). Under the conditions of the study, BMHCA was considered to be non-clastogenic in the *in vitro* micronucleus test. The clastogenic activity of *p-t*-butyl-α-methylhydrocinnamic aldehyde 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 IP injection to groups of male and female IRC mice. Doses of 150, 300, or 600 mg/kg body weight 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, *p-t*-butyl-α-methylhydrocinnamic aldehyde 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, *p-t*-butyl-α-methylhydrocinnamic aldehyde does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/20/18.

10.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 3-(*p-tert*-butylphenyl)-2-methylpropanol or any read-across materials. The total systemic exposure to 3-(*p-tert*-butylphenyl)-2-methylpropanol is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3-(*p-tert*-butylphenyl)-2-methylpropanol or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3-(*p-tert*-butylphenyl)-2-methylpropanol

(9.1 μg/kg bw/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: None.

Literature Search and Risk Assessment Completed On: 11/14/18.

10.1.3. Reproductive Toxicity

There are no developmental toxicity data and insufficient reproductive toxicity data on 3-(*p-tert*-butylphenyl)-2-methylpropanol or on any read-across materials. The total systemic exposure to 3-(*p-tert*-butylphenyl)-2-methylpropanol is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data and insufficient reproductive toxicity data on 3-(*p-tert*-butylphenyl)-2-methylpropanol or on any read-across materials that can be used to support the developmental and reproductive toxicity endpoints. The total systemic exposure to 3-(*p-tert*-butylphenyl)-2-methylpropanol (9.1 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2011.

Literature Search and Risk Assessment Completed On: 11/16/18.

10.1.4. Skin sensitization

Based on the existing data on the read-across material, 2-(4-methylphenoxy)ethanol (CAS # 15149-10-7), the target material, 3-(*p-tert*-Butylphenyl)-2-methylpropanol, does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. No skin sensitization studies are available for 3-(*p-tert*-Butylphenyl)-2-methylpropanol. Based on the existing data and read-across material 2-(4-methylphenoxy)ethanol (CAS # 15149-10-7; see Section V), the target material, 3-(*p-tert*-Butylphenyl)-2-methylpropanol, does not present a concern for skin sensitization. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD toolbox v4.2). In a murine local lymph node assay, read-across material 2-(4-methylphenoxy)ethanol was found to be not sensitizing when tested up to 40% (10000 μg/cm^2) (RIFM, 2002). Additionally, in 2 separate confirmatory human repeat insult patch tests with 1938 μg/cm^2 of the read-across material 2-(4-methylphenoxy)ethanol, no reactions indicative of sensitization was observed in any of the 10 and 34 volunteers (RIFM, 1971; RIFM, 1972).

Based on weight of evidence (WoE) from structural analysis and the read-across material 2-(4-methylphenoxy)ethanol, the target material 3-(*p-tert*-Butylphenyl)-2-methylpropanol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/19/18.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, 3-(*p-tert*-butylphenyl)-2-methylpropanol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 3-(*p-tert*-butylphenyl)-2-methylpropanol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 3-(*p-tert*-butylphenyl)-2-methylpropanol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant 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: 11/04/18.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The material, 3-(*p-tert*-butylphenyl)-2-methylpropanol, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 3-(*p-tert*-butylphenyl)-2-methylpropanol. Based on the Creme RIFM Model, the inhalation exposure is 0.012 mg/day. This exposure is 116.6 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: 11/01/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3-(*p-tert*-butylphenyl)-2-methylpropanol was performed following the RIFM Environmental Framework (Salvito et al., 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, 3-(*p-tert*-butylphenyl)-2-methylpropanol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 3-(*p-tert*-butylphenyl)-2-methylpropanol as possibly persistent or 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.

10.2.2. Risk assessment

Based on the current VoU (2015), 3-(*p-tert*-butylphenyl)-2-methylpropanol presents no risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.2.1.1. Biodegradation. No data available.

10.2.2.1.2. Ecotoxicity. No data available.

10.2.2.1.3. Other available data. 3-(*p-tert*-Butylphenyl)-2-methylpropanol has been registered under REACH and the following additional data is available:

A ready biodegradability study was conducted according to the OECD 301B method (CO_2 evolution), and biodegradation of 80.7% was observed after 28 days.

10.2.3. 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.

	LC_{50} (Fish) (mg/L)	EC_{50} (*Daphnia*) (mg/L)	EC_{50} (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.365			1,000,000	0.002365	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.38	4.38
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	Not reported
Risk Characterization: PEC/PNEC	**< 1**	**N/A**

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

The RIFM PNEC is 0.002365 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/14/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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. 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 04/20/20.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111425.

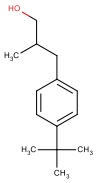
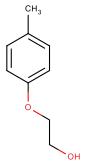
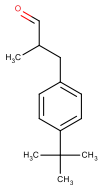
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018) and skin sensitization was predicted using Toxtree.
- The major metabolites for the target substance and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	3-(*p-tert*-Butylphenyl)-2-methylpropanol	2-(4-Methylphenoxy) ethanol	*p-t*-Butyl-alpha-methylhydrocinnamic aldehyde
CAS No.	56107-04-1	15149-10-7	80-54-6
Structure			
Similarity (Tanimoto Score)		0.27	0.75
Read-across Endpoint		• Skin Sensitization	• Genotoxicity
Molecular Formula	$C_{14}H_{22}O$	$C_9H_{12}O_2$	$C_{14}H_{20}O$
Molecular Weight	206.32	152.19	204.31
Melting Point (°C, EPI Suite)	61.11	39.43	46.29
Boiling Point (°C, EPI Suite)	298.56	261.19	280.03
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.00909	0.156	0.477
Log Kow (KOWWIN v1.68 in EPI Suite)	4.38	1.65	4.36
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	23.65	9407	7.859
Jmax (μg/cm^2/h, SAM)	8.58	144.01	4.17
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.33E-001	1.73E-003	2.53E+000
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found		• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes		• Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes|Schiff base formers|Schiff base formers ≫ Direct Acting
Carcinogenicity (ISS)	• Non-carcinogen (moderate reliability)		• Carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1	• No alert found		• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found		• Simple aldehyde
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found		• Simple aldehyde
Oncologic Classification	• Not classified		• Aldehyde Type Compounds
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found	• No alert found	
Protein binding (OECD)	• No alert found	• No alert found	

Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 3-(*p-tert*-butylphenyl)-2-methylpropanol (CAS # 56107-04-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 2-(4-methylphenoxy)ethanol (CAS # 15149-10-7) and *p-t*-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

The metabolism of the target material 3-(*p-tert*-butylphenyl)-2-methylpropanol (CAS # 56107-04-1) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolically oxidized to *p-t*-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6) in the first step with 0.95 probability. Hence, *p-t*-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6) can be used a read-across analog for the target material. Read-across analog was in domain for the *in vivo* rat and in domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19).

Conclusions

- 2-(4-Methylphenoxy)ethanol (CAS # 15149-10-7) was used as a read-across analog for the target material 3-(*p-tert*-butylphenyl)-2-methylpropanol (CAS # 56107-04-1) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to a class of aryl primary alkyl alcohols.
  - o The target substance and the read-across analog share alkyl substituted phenyl ring structures with primary alcohols.
  - o The key difference between the target substance and the read-across analog is that the primary alcohol in the target substance is a 2-methylpropanol ring substituent, whereas in the read-across analog, the alcohol is a 2-hydroxyethoxy ring substituent. These alcohols have similar potential metabolism and reactivity. The substituents are secondary differences; the target has a *tert*-butyl group para to the alkyl alcohol, whereas the analog has a methyl in the para position. These structural differences are toxicologically insignificant for the skin sensitization endpoint.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target substance corresponds to skin absorption $\leq 40\%$ and J_{max} for the read-across analog corresponds to skin absorption $\leq 80\%$. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- *p-t*-Butyl-alpha-methylhydrocinnamic aldehyde (CAS # 80-54-6) was used as a read-across analog for the target material 3-(*p-tert*-butylphenyl)-2-methylpropanol (CAS # 56107-04-1) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar alkyl aromatic compounds.
  - o The target substance and the read-across analog share *p-t*-butyl-methylpropyl phenyl structures.
  - o The key difference between the target substance and the read-across analog is that the target material is a methylpropanol whereas the read-across analog is a methylpropanal. This structural difference makes the aldehyde more reactive than the alcohol, which is appropriate for the genotoxicity endpoint.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.

- o Compared to the target substance, the read-across analog has a structure alerts as an aldehyde type compound and a carcinogen by the ISS model. The read-across is expected to be more reactive compared to the target. The data described in the genotoxicity section confirm that the material does not pose a concern for genetic toxicity under current level of use. Therefore, the predictions are superseded by data.
- o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Di Sotto, A., Maffei, F., Hrelia, P., Di Giacomo, S., Pagano, E., Borrelli, F., Mazzanti, G., 2014. Genotoxicity assessment of some cosmetic and food additives. Regul. Toxicol. Pharmacol. 68 (1), 16–22.

ECHA, 2011a. Registration dossier 2-(4-tert-Butylbenzyl)propionaldehyde. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/13572.

ECHA, 2011b. Registration dossier 3-(p-tert-butylphenyl)-2-methylpropanol. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/1600.

ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. Read-across assessment framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc), 1971. Repeated Insult Patch Test with 2-(4-methylphenoxy)ethanol in Humans. Unpublished Report from International Flavors and Fragrances. RIFM Report Number 55017. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1972. Repeated Insult Patch Test with 2-(4-methylphenoxy)ethanol in Humans. Unpublished Report from International Flavors and Fragrances. RIFM Report Number 55018. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1984. Mutagenicity Evaluation of P-T-Butyl-Alpha-Methylhydrocinnamic Aldehyde (Lilial) in the Salmonella/mammalian Microsome Plate Incorporation Assay (Ames Test). Unpublished Report from Givaudan-Roure Corporation. RIFM Report Number 34333. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2000. *In Vitro* Mammalian Chromosome Aberration Test of Para-Tert-Butyl-Alpha-Methylhydrocinnamic Aldehyde. RIFM Report Number 35685. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2000. Mammalian Erythrocyte Micronucleus Test of Para-Tert-Butyl-Alpha-Methylhydrocinnamic Aldehyde. RIFM Report Number 35691. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2002. Murine Local Lymph Node Assay with 2-(4-methylphenoxy)ethanol. Unpublished Report from Firmenich SA. RIFM Report Number 41989. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2010. Gene Mutation Assay in Chinese Hamster V79 Cells in Vitro (V79/HPRT) with P-T-Butyl-Alpha-Methylhydrocinnamic Aldehyde (Lysmeral). Unpublished Report from BASF SE. RIFM Report Number 60847. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2011. Screening Study on Testes Toxicity in Male Wistar Rats. Oral Administration (Gavage). Unpublished Report from BASF. RIFM Report Number 59014. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of 3-(p-Tert-Butylphenyl)-2-Methylpropanol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 66093. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016. Exposure Survey 10. March 2016.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

SCCS, 2017. Scientific committee on consumer safety opinion on the safety of butylphenyl methylpropional (p- BMHCA) in 21 cosmetic products - submission II, december 2017. Retrieved from. https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_213.pdf.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.