



Short Review

RIFM fragrance ingredient safety assessment, $\beta,\beta,3$ -trimethyl benzenepropanol, CAS Registry Number 103694-68-4

A.M. Api^a, D. Belsito^b, S. Biserta^a, D. Botelho^a, M. Bruze^c, G.A. Burton Jr.^d, J. Buschmann^e, M.A. Cancellieri^a, M.L. Dagli^f, M. Date^a, W. Dekant^g, C. Deodhar^a, A.D. Fryer^h, S. Gadhia^a, L. Jones^a, K. Joshi^a, A. Lapczynski^a, M. Lavelle^a, D.C. Lieblerⁱ, M. Na^a, D. O'Brien^a, A. Patel^a, T.M. Penning^j, G. Ritacco^a, F. Rodriguez-Ropero^a, J. Romine^a, N. Sadekar^a, D. Salvito^a, T.W. Schultz^k, F. Siddiqi^a, I.G. Sipes^l, G. Sullivan^{a,*}, Y. Thakkar^a, Y. Tokura^m, S. Tsang^a

^a Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA

^b Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA

^c Member Expert Panel, Malmö University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmö, SE, 20502, Sweden

^d Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 48109, USA

^e Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany

^f Member Expert Panel, University of São Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, São Paulo, CEP 05508-900, Brazil

^g Member Expert Panel, University of Würzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany

^h Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA

ⁱ Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA

^j Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA

^k Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

^l Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

^m Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

ARTICLE INFO

Keywords:

Genotoxicity
Repeated dose, developmental, and reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory Toxicity
Environmental safety

* Corresponding author.

E-mail address: gsullivan@rifm.org (G. Sullivan).

<https://doi.org/10.1016/j.fct.2019.110650>

Received 15 April 2019; Accepted 25 June 2019

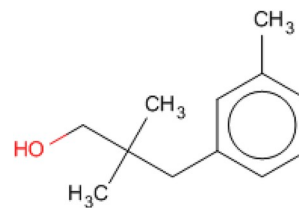
Available online 26 June 2019

0278-6915/© 2019 Elsevier Ltd. All rights reserved.

Version: 030419. This version replaces any previous versions.

Name: $\beta,\beta,3$ -Trimethyl benzenepropanol

CAS Registry Number: 103694-68-4



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

Creame RIFM Model - The Creame 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; Safford et al., 2015a; Safford et al., 2017; Comiskey et al., 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

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 et al., 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.

$\beta,\beta,3$ -Trimethyl benzenepropanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that $\beta,\beta,3$ -trimethyl benzenepropanol is not genotoxic. Data provide a calculated MOE > 100 for the repeated dose toxicity endpoint and a NESIL of $9900 \mu\text{g}/\text{cm}^2$ for the skin sensitization endpoint. The developmental and reproductive toxicity and the local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material, and the exposure to $\beta,\beta,3$ -trimethyl benzenepropanol is below the TTC ($0.03 \text{ mg}/\text{kg}/\text{day}$ and $1.4 \text{ mg}/\text{day}$, respectively). The phototoxicity/photoallergenicity endpoint was evaluated based on data and UV Spectra; $\beta,\beta,3$ -trimethyl benzenepropanol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; $\beta,\beta,3$ -trimethyl benzenepropanol 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.

Repeated Dose Toxicity: NOAEL = $19 \text{ mg}/\text{kg}/\text{day}$.

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

Skin Sensitization: NESIL = $9900 \mu\text{g}/\text{cm}^2$.

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.

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

(RIFM, 1987a; RIFM, 1987f)

(RIFM, 1987e)

(RIFM, 2005; RIFM, 2007)

(UV Spectra; RIFM Database)

Environmental Safety Assessment**Hazard Assessment:****Persistence:** Critical Measured Value: 10% (OECD 301B)

(RIFM, 2000)

Bioaccumulation: Screening-level: 50.69 L/kg

(EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 9-h Fish LC50: 9.0 mg/L

(RIFM, 1987d)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards**Risk Assessment:****Screening-level:** PEC/PNEC (North America and Europe) > 1

(RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 96-h Fish LC50: 9.0 mg/L

(RIFM, 1987d)

RIFM PNEC is: 9.0 µg/L

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

1. Identification

- Chemical Name:** $\beta,\beta,3$ -Trimethyl benzenepropanol
- CAS Registry Number:** 103694-68-4
- Synonyms:** Benzenepropanol, $\beta,\beta,3$ -trimethyl-; 2,2-Dimethyl-3-(3-methylphenyl)propanol; 2,2-Dimethyl-3-(3-tolyl)propan-1-ol; Majantol; Muguetol B; Benzenepropanol; $\beta,\beta,3$ -Trimethyl benzenepropanol
- Molecular Formula:** $C_{12}H_{18}O$
- Molecular Weight:** 178.28
- RIFM Number:** 6320

2. Physical data

- Boiling Point:** 531.7 K (mean) at 1013.3 hPa (RIFM, 1987j), 277.04 °C (EPI Suite)
- Flash Point:** 132 °C at 101.3 kPa (RIFM, 1987i)
- Log Kow:** Log Pow = 3.40 (RIFM, 2001), 3.48 (EPI Suite)
- Melting Point:** 51.06 °C (EPI Suite)
- Water Solubility:** 265.8 mg/L (RIFM, 1987h), 256.8 mg/L (RIFM, 2001), 195.3 mg/L (EPI Suite)
- Specific Gravity:** 0.95500 to 0.96500 @ 25.00 °C*
- Vapor Pressure:** 92.3 hPa at 451.7 K (RIFM, 1987k), 366.9 hPa at 501.3 K (RIFM, 1987k), 2.8e-2 hPa at 293.15 K (corrected) (RIFM, 1987k), 12.1e-2 hPa at 313.15 K (corrected) (RIFM, 1987k), 0.000335 mm Hg @ 25 °C (EPI Suite), 0.000168 mm Hg @ 20 °C (EPI Suite v4.0)
- UV Spectra:** No significant absorbance in the region of 290–700 nm; molar absorption below the benchmark ($1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$)
- Appearance/Organoleptic:** Colorless to pale yellow clear oily liquid with medium floral scent; floral lily of the valley green tropical*

*<http://www.thegoodscentscompany.com/data/rw1020401.html>, retrieved 08/01/13.

3. Exposure

- Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
- 95th Percentile Concentration in Hydroalcohols:** 0.055% (RIFM, 2015d)
- Inhalation Exposure*:** 0.001 mg/kg/day or 0.073 mg/day (RIFM, 2015d)
- Total Systemic Exposure**:** 0.013 mg/kg/day (RIFM, 2015d)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- Inhalation:** Assumed 100%

5. Computational toxicology evaluation

- Cramer Classification:** Class I, Low (Expert Judgment)

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

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was also determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further detail.

- Analogs Selected:
 - Genotoxicity:** None
 - Repeated Dose Toxicity:** None
 - Developmental and Reproductive Toxicity:** None
 - Skin Sensitization:** None
 - Phototoxicity/Photoallergenicity:** None
 - Local Respiratory Toxicity:** None
 - Environmental Toxicity:** None
- Read-across Justification:** None

6. Metabolism

Not relevant 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)

$\beta,\beta,3$ -Trimethyl benzenepropanol 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 on 07/17/13 (ECHA, 2012a).

9. Conclusion

The maximum acceptable concentrations^a in finished products for $\beta,\beta,3$ -trimethyl benzenepropanol are detailed below.

IFRA Category ^b	Description of Product Type	Maximum Acceptable Concentrations ^a in Finished Products (%)
1	Products applied to the lips (lipstick)	0.041
2	Products applied to the axillae	0.15
3	Products applied to the face/body using fingertips	0.021
4	Products related to fine fragrances	1.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.35
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.062
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.041
5D	Baby cream, oil, talc	0.014
6	Products with oral and lip exposure	0.0010
7	Products applied to the hair with some hand contact	0.041
8	Products with significant ano-genital exposure (tampon)	0.014
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.12
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.12
10B	Aerosol air freshener	0.29
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.014
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	6.6

Note: ^aMaximum 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 $\beta,\beta,3$ -trimethyl benzenepropanol, the basis was the reference dose of 0.19 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 9900 $\mu\text{g}/\text{cm}^2$.

^bFor a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, $\beta,\beta,3$ -trimethyl benzenepropanol does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. $\beta,\beta,3$ -Trimethyl benzenepropanol was tested using the BlueScreen assay and found negative for genotoxicity in the presence and absence of metabolic activation (RIFM, 2013). The mutagenicity of $\beta,\beta,3$ -trimethyl benzenepropanol was assessed in an *in vitro* Ames study conducted in compliance with GLP regulations and in compliance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 were treated with $\beta,\beta,3$ -trimethyl benzenepropanol in dimethyl sulfoxide (DMSO) at concentrations ranging from 0 to 1000 $\mu\text{g}/\text{plate}$ in the presence and

absence of metabolic activation. No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, at any dose, with or without metabolic activation (RIFM, 1987a). Under the conditions of the study, $\beta,\beta,3$ -trimethyl benzenepropanol was considered not mutagenic in the Ames test.

The clastogenicity of $\beta,\beta,3$ -trimethyl benzenepropanol was assessed in an *in vivo* mouse micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 474. Male and female NMRI mice were dosed at concentrations levels up to 1000 mg/kg body weight of $\beta,\beta,3$ -trimethyl benzenepropanol in 20 mL/kg isotonic saline via a single intraperitoneal injection. No significant increase in the micronucleated polychromatic erythrocytes in the test article treated groups relative to the respective vehicle control group was observed in male or female mice at 24, 48, or 72 h after the dose administration (RIFM, 1987f). Under the conditions of the study, $\beta,\beta,3$ -trimethyl benzenepropanol was concluded to be negative in the mouse micronucleus assay.

Based on the available data, $\beta,\beta,3$ -trimethyl benzenepropanol does not present a concern for genotoxic potential.

Additional References: RIFM, 1987a; RIFM, 1987b; RIFM, 2013.

Literature Search and Risk Assessment Completed On: 02/14/17.

10.1.2. Repeated dose toxicity

The margin of exposure for $\beta,\beta,3$ -trimethyl benzenepropanol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on $\beta,\beta,3$ -trimethyl benzenepropanol for the repeated dose toxicity endpoint. $\beta,\beta,3$ -Trimethyl benzenepropanol has an OECD 407/GLP 28-day dietary subchronic toxicity study conducted in Wistar rats. Groups of 5 rats/sex/dose were fed diets containing 0, 800, 3000, or 10000 ppm of $\beta,\beta,3$ -trimethyl-benzenepropanol for 28 days. The NOAEL was considered to be 800 ppm or 58 mg/kg/day, based on increased plasma sodium levels and increased liver and kidney weights among higher dose group animals (RIFM, 1987e).

A default safety factor of 3 was used when deriving a NOAEL from a 28 day OECD 407 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 58/3 or 19 mg/kg/day.

Therefore, the $\beta,\beta,3$ -trimethyl benzenepropanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the $\beta,\beta,3$ -trimethyl benzenepropanol NOAEL in mg/kg/day by the total systemic exposure to $\beta,\beta,3$ -trimethyl benzenepropanol, 19/0.013 or 1462.

In addition, the total systemic exposure to $\beta,\beta,3$ -trimethyl benzenepropanol (13 $\mu\text{g}/\text{kg}/\text{day}$) is below the TTC (30 $\mu\text{g}/\text{kg}/\text{bw}/\text{day}$; Kroes

Table 1

Data Summary for $\beta,\beta,3$ -trimethyl benzenepropanol.

LLNA weighted mean EC3 value [No. Studies]	Potency Classification Based on Animal Data ^a	Human Data			
		NOEL-HRIPT (induction) $\mu\text{g}/\text{cm}^2$	NOEL-HMT (induction) $\mu\text{g}/\text{cm}^2$	LOEL ^b (induction) $\mu\text{g}/\text{cm}^2$	WoE NESIL ^c $\mu\text{g}/\text{cm}^2$
> 7500 [1]	Weak	9917	NA	NA	9900

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.

et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section 9 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 0.19 mg/kg/day.

The RfD for $\beta,\beta,3$ -trimethyl benzenepropanol was calculated by dividing the NOAEL of 19 mg/kg/day by the uncertainty factor, $100 = 0.19$ mg/kg/day.

* The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/15/17.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on $\beta,\beta,3$ -trimethyl benzenepropanol or on any read-across materials. The total systemic exposure to $\beta,\beta,3$ -trimethyl benzenepropanol 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 or reproductive toxicity data on $\beta,\beta,3$ -trimethyl benzenepropanol or on any read-across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to $\beta,\beta,3$ -trimethyl benzenepropanol (13 $\mu\text{g/kg/day}$) is below the TTC (30 $\mu\text{g/kg/day}$; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/15/17.

10.1.4. Skin sensitization

Based on the available data, $\beta,\beta,3$ -trimethyl benzenepropanol is considered to be a weak skin sensitizer with a defined NESIL of 9900 $\mu\text{g/cm}^2$.

10.1.4.1. Risk assessment. Based on the existing data, $\beta,\beta,3$ -trimethyl benzenepropanol is considered a weak skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). $\beta,\beta,3$ -Trimethyl benzenepropanol was found to be negative in an *in vitro* Direct Peptide Reactivity Assay (DPRA) (RIFM, 2015a). However, $\beta,\beta,3$ -trimethyl benzenepropanol was found to be positive in the KeratinoSens, h-CLAT, and U-Sens assay (RIFM, 2015b; RIFM, 2014; RIFM, 2015c). In 1 murine local lymph node assay (LLNA), $\beta,\beta,3$ -trimethyl benzenepropanol was found to be sensitizing at 30% (7500 $\mu\text{g/cm}^2$) with a Stimulation Index of 3.07 (RIFM, 2002a). In 3 other LLNA studies conducted according to OECD and GLP guidelines, $\beta,\beta,3$ -trimethyl benzenepropanol was found to be non-sensitizing up to 100% (RIFM, 2009; RIFM, 2008b; RIFM, 2002b). In guinea pig maximization tests, no reactions indicative of sensitization were observed with $\beta,\beta,3$ -trimethyl benzenepropanol (RIFM, 1987b; RIFM, 1985a). Similarly, in confirmatory human repeated insult patch tests (HRIPT), up to 18% or 9917 $\mu\text{g/cm}^2$ $\beta,\beta,3$ -trimethyl benzenepropanol in 3:1 diethyl phthalate did not produce reactions indicative of sensitization in any of the volunteers (RIFM, 2007; RIFM, 2005). The available data demonstrate that $\beta,\beta,3$ -trimethyl benzenepropanol is a

weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 9900 $\mu\text{g/cm}^2$ (Table 1). Section 9 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 0.19 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/19/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available data and UV Spectra, $\beta,\beta,3$ -trimethyl benzenepropanol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. 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 et al., 2009). Additionally, no phototoxic/allergic responses were observed in guinea pigs following topical application of a 5% solution of $\beta,\beta,3$ -trimethyl benzenepropanol followed by exposure to UV (RIFM, 1985b; RIFM, 1985c). It should be noted that the studies conducted failed to include appropriate control groups, and the UV irradiation dose may not have been suitable to evaluate phototoxicity and photoallergenicity. Based on the lack of absorbance, $\beta,\beta,3$ -trimethyl benzenepropanol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra. 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 $\text{L mol}^{-1} \cdot \text{cm}^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/17/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for $\beta,\beta,3$ -trimethyl benzenepropanol 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 $\beta,\beta,3$ -trimethyl benzenepropanol. Based on the Creme RIFM Model, the inhalation exposure is 0.073 mg/day. This exposure is 19.2 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Key Studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/16/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of $\beta,\beta,3$ -trimethyl benzenepropanol 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, $\beta,\beta,3$ -trimethyl benzenepropanol 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 v4.1 identified $\beta,\beta,3$ -trimethyl benzenepropanol as being 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012b). 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on the current VoU (2015), $\beta,\beta,3$ -trimethyl benzenepropanol presents a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key Studies

10.2.1.2.1. Biodegradation. RIFM, 2000: A biodegradation study was conducted on sludge using a manometric respirometry test according to the OECD 301B method. The test material was incubated with activated sludge at a constant temperature for 56 days. $\beta,\beta,3$ -Trimethyl benzenepropanol underwent 16% degradation at the end of the extended 56-day study period.

RIFM, 1987c: The biodegradability of the test material was tested according to OECD Guideline 301 B "Ready Biodegradability (Modified Sturm Test)." Biodegradation of 4% was observed after 28 days.

10.2.1.2.2. Ecotoxicity. RIFM, 1987g: An acute toxicity study was conducted to determine the immobilizing properties of the test material in *Daphnia magna* according to the OECD 202 guidelines. The 48-h EC50 of the test material was 19 mg/L.

RIFM, 1987d: The acute toxicity of the test material to the Zebrafish *Brachydanio rerio* was investigated under static conditions with continuous aeration according to the OECD 203 guidelines. The 96-h LC50 was reported to be 9.0 mg/L.

RIFM, 1988: The acute toxicity of the test material to the Zebrafish *Brachydanio rerio* was evaluated according to the OECD 203 method under flow-through conditions. Under the conditions of this study, the LC50 was reported to be 19 mg/L.

RIFM, 2001: A 72-h algae acute toxicity test was conducted with test material according to the OECD 201 method. The EbC50 was calculated to be 19 mg/L, the ErC50 was calculated to be 27 mg/L, and the NOEC for both rate-related inhibition and biomass inhibition was reported to be 7.2 mg/L.

Other available data:

$\beta,\beta,3$ -Trimethyl benzenepropanol has been registered under REACH with no additional data.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ($\mu\text{g/L}$)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>14.55</u>			1,000,000	0.0145	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	6.918	<u>4.502</u>	5.892	10,000	0.45	Aldehydes
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	<u>9.0</u>			1,000	9.0	
<i>Daphnia</i>		19				
Algae		19				

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

Exposure	Europe (EU)	North America (NA)
Log K _{ow} used	3.4	3.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	< 1	< 1

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

The RIFM PNEC is 9.0 µg/L. The revised PEC/PNECs for EU and NA 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: 02/21/19.

11. 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>
- **TOXNET:** <https://toxnet.nlm.nih.gov/>
- **IARC:** <https://monographs.iarc.fr>
- **OECD SIDS:** <https://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/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/>

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 03/04/19.

Conflicts of 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 a small honorarium for time spent reviewing the subject work.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Appendix

Explanation of Cramer Class

Due to potential discrepancies with the current *in silico* tools (Bhatia

et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

- Q1. A normal constituent of the body? No
- Q2. Contains functional groups associated with enhanced toxicity? No
- Q3. Contains elements other than C, H, O, N, divalent S? No
- Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
- Q6. Benzene derivative with certain substituents? No
- Q7. Heterocyclic? No
- Q16. Common terpene? No
- Q17. Readily hydrolyzed to a common terpene? No
- Q19. Open chain? No
- Q23. Aromatic? Yes
- Q27. Rings with substituents? Yes
- Q28. More than one aromatic ring? No
- Q30. Aromatic Ring with complex substituents? No
- Q18. One of the list (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity)? No. Class Low (Class I)

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.
- Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR toolbox and expert judgment. *Regul. Toxicol. Pharmacol.* 71 (1), 52–62.
- 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.
- 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.
- Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. *Food Cosmet. Toxicol.* 16 (3), 255–276.
- ECHA, 2012a. Registration dossier 3-(2,2-Dimethyl-3-hydroxypropyl)toluene. Retrieved from: <https://echa.europa.eu/registration-dossier/-/registered-dossier/6048>.
- ECHA, 2012b. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. <http://echa.europa.eu/>.
- 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.
- RIFM (Research Institute for Fragrance Materials, Inc), 1985a. Delayed Contact Hypersensitivity of .beta.,.beta.,3-trimethyl Benzenepropanol (Muguetol B) in guinea-pigs Modified by B. Magnusson and A. M. Kligman. Unpublished report from Symrise GmbH & Co. KG. RIFM report number 49522. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1985b. .beta.,.beta.,3-Trimethyl Benzenepropanol (Muguetol B): Experimental Investigation on Phototoxic Effect in guinea Pigs. Unpublished report from Symrise. RIFM report number 58665. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1985c. .beta.,.beta.,3-Trimethyl Benzenepropanol (Muguetol B): Experimental Investigation on Photo-Sensitizing Effect in guinea-pigs. Unpublished report from Symrise. RIFM report number 58683.

- RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987a. Mutagenicity Evaluation of Benzenepropanol, .beta.,.beta.,3-trimethyl- in the Ames Salmonella/Microsome Plate Assay. Unpublished report from Symrise GmbH & Co. KG. RIFM report number 49524. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987b. .beta.,.beta.,3-Trimethyl Benzenepropanol (Majantol): Guinea Pig Sensitization Test. Unpublished report from Symrise. RIFM report number 58684. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987c. Determination of the Biodegradability of .beta.,.beta.,3-trimethyl Benzenepropanol (Majantol). Unpublished report from Symrise. RIFM report number 58685. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987d. Investigation of the Lethal Effects of .beta.,.beta.,3-trimethyl Benzenepropanol (Majantol) to the Zebra Fish (Branchydanio Rerio). Unpublished report from Symrise. RIFM report number 58686. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987e. Sub-acute (28-Day) Oral Toxicity Study with .beta.,.beta.,3-trimethyl Benzenepropanol (Majantol) in Rats. Unpublished report from Symrise. RIFM report number 58687. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987f. In Vivo Micronucleus Test in Mice of .beta.,.beta.,3-trimethyl Benzenepropanol (Majantol). Unpublished report from Symrise. RIFM report number 58688. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987g. Investigation of .beta.,.beta.,3-trimethyl Benzenepropanol (Majantol) in the Acute Immobilisation Test on Daphnia Magna. Unpublished report from Symrise. RIFM report number 58689. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987h. .beta.,.beta.,3-Trimethyl Benzenepropanol (Majantol): Water Solubility Test. Unpublished report from Symrise. RIFM report number 60269. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987i. .beta.,.beta.,3-Trimethyl Benzenepropanol (Majantol): Flash Point. Unpublished report from Symrise. RIFM report number 60270. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987j. .beta.,.beta.,3-Trimethyl Benzenepropanol (Majantol): Boiling Point. Unpublished report from Symrise. RIFM report number 61010. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1987k. .beta.,.beta.,3-Trimethyl Benzenepropanol (Majantol): Vapor Pressure. Unpublished report from Symrise. RIFM report number 61012. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1988. Investigation of the Lethal Effects of .beta.,.beta.,3-trimethyl Benzenepropanol (Majantol) to the Zebra-Fish (Branchydanio Rerio). Unpublished report from Symrise. RIFM report number 65532. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2000. Ready Biodegradability Test with .beta.,.beta.,3-trimethyl Benzenepropanol (Majantol). Unpublished report from Symrise. RIFM report number 58691. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2001. .beta.,.beta.,3-Trimethyl Benzenepropanol (Majantol): Alga, Growth Inhibition Test with Scenedesmus Subspicatus, 72 H. Unpublished report from Symrise. RIFM report number 58692. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2002a. .beta.,.beta.,3-Trimethyl Benzenepropanol (Majantol): Local Lymph Node Assay. Unpublished report from Symrise. RIFM report number 58693. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2002b. Benzenepropanol, .beta.,.beta.,3-trimethyl-: Local Lymph Node Assay. Unpublished report from Symrise GmbH & Co. KG. RIFM report number 49523. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2005. Repeated Insult Patch Test with Benzenepropanol, .beta.,.beta.,3-trimethyl- (Majantol). Unpublished report from Symrise GmbH & Co. KG. RIFM report number 49526. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2007. Repeated Insult Patch Test with .beta.,.beta.,3-Trimethyl Benzenepropanol (Majantol). Unpublished report from Symrise GmbH & Co. KG. RIFM report number 53799. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2008a. Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. RIFM report number 55663. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2008b. .beta.,.beta.,3-Trimethyl Benzenepropanol (Majantol): Local Lymph Node Assay. Unpublished report from Symrise. RIFM report number 60265. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2009. .beta.,.beta.,3-Trimethyl Benzenepropanol (Majantol): Local Lymph Node Assay. Unpublished report from Symrise. RIFM report number 60266. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of .beta.,.beta.,3-trimethyl Benzenepropanol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65955. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2014. .beta.,.beta.,3-Trimethyl Benzenepropanol: in Vitro Skin Sensitization Human Cell Line Activation Test (H-CLAT). RIFM report number 68414. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2015a. Direct Peptide Reactivity Assay (DPRA) of Alpha-Amylcinnamyl Alcohol, Benzyl Cinnamate, Butyl Acrylate, P-Tert-Butyldihydrocinnamaldehyde, Carvone and 1-cyclohexylethyl 2-butenolate. RIFM report number 69649. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2015b. Induction of Antioxidant-Response Element Dependent Gene Activity Cytotoxicity (Using MTT) in the Keratinocyte ARE- Reporter Cell Line Keratinosens. RIFM report number 69647. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2015c. p-tert-Butyldihydrocinnamaldehyde: U-SENS Skin Sensitization Method. RIFM report number 68249. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2015d. Exposure Survey 07. May 2015.
- 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.
- 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.
- 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.