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Short Review

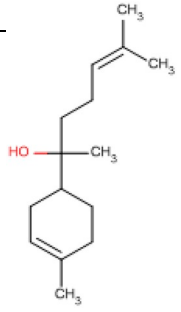
RIFM fragrance ingredient safety assessment, α-bisabolol, CAS registry number 515-69-5

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. Liebler[i], 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, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, 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 Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo CEP, 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, 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*

Version: 032619. This version replaces any previous versions.

Name: α-Bisabolol
CAS Registry Number: 515-69-5



Additional CAS Numbers*:
78148-59-1 (−)-epi-α-Bisabolol
23178-88-3 (+)-α-Bisabolol
23089-26-1 α-Bisabolol
76738-75-5 (+)-epi-α-Bisabolol
72691-24-8 3-Cyclohexene-1-methanol, α,4-dimethyl-α-(4-methyl-3-penten-1-yl)-*Included because they are a commercial mixture

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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

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

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DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
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 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.

α-Bisabolol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that α-bisabolol is not genotoxic. Data on α-bisabolol provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and developmental toxicity endpoints. The 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 α-bisabolol is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from α-bisabolol provided a No Expected Sensitization Induction Level (NESIL) of 5500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet (UV) spectra; α-bisabolol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; α-bisabolol 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 genotoxic. (RIFM, 2002; CIR, 1999)

Repeated Dose Toxicity: NOAEL = 200 mg/kg/day. RIFM (1996)

Developmental and Reproductive Toxicity: Developmental NOAEL = 980 mg/kg/day. No reproductive NOAEL. Exposure is below the TTC. (Habersang et al., 1979)

Skin Sensitization: NESIL = 5500 μg/cm^2. (RIFM, 1999a; RIFM, 2010a; RIFM, 2010b)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM Database; RIFM, 1977; RIFM, 1983)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 62% (42 days; OECD 301F) RIFM (1992)

Bioaccumulation: Screening-level: 2403 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: LC50: 0.222 mg/L (RIFM Framework; Salvito et al., 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 et al., 2002)

Critical Ecotoxicity Endpoint: LC50: 0.222 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.000222 μg/L

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

1. Identification

Chemical Name: α-Bisabolol	Chemical Name: α-Bisabolol	Chemical Name: (+)-α-Bisabolol
CAS Registry Number: 515-69-5 **Synonyms:** α-Bisabolol; 3-Cyclohexene-1-methanol,.α.,4-dimethyl-α-(4-methyl-3-pentenyl)-, (R*,R*)-; (R*,R*)-.α.,4-Dimethyl-α-(4-methyl-3-pentenyl)cyclohex-3-ene-1-methanol; Bisabolol; 6-Methyl-2-(-4-methylcyclohex-3-en-1-yl)hept-5-en-2-ol; Dragosantol; Bisabolol nat. roh (Candela-Öl); -α-Bisabolol rac.; Dragosantol 100; 6-Methyl-2-(4-methyl-3-cyclohexen-1-yl)-5-hepten-2-ol **Molecular Formula:** $C_{15}H_{26}O$ **Molecular Weight:** 222.37 **RIFM Number:** 5184 **Stereochemistry:** Two stereocenters and 4 stereoisomers	**CAS Registry Number:** 23089-26-1 **Synonyms:** α-(−)-Bisabolol; (−)-α-Bisabolol; (−)-(1′S,2S)-α-Bisabolol; (−)-(4S,8S)-α-Bisabolol; 5-Hepten-2-ol, 6-methyl-2-(4-methyl-3-cyclohexen-1-yl), (−)-; (2R)-6-Methyl-2-[(1R)-4-methylcyclohex-3-en-1-yl]hept-5-en-2-ol; α-Bisabolol **Molecular Formula:** $C_{15}H_{26}O$ **Molecular Weight:** 222.37 **RIFM Number:** 5184 **Stereochemistry:** Two stereocenters and 4 stereoisomers	**CAS Registry Number:** 23178-88-3 **Synonyms:** 3-Cyclohexene-1-methanol, α,4-dimethyl-α-(4-methyl-3-penten-1-yl)-, (αR,1R)-; (+)-α-Bisabolol **Molecular Formula:** $C_{15}H_{26}O$ **Molecular Weight:** 222.37 **RIFM Number:** 5184 **Stereochemistry:** Two stereocenters and 4 stereoisomers
Chemical Name: (−)-epi-α-Bisabolol	**Chemical Name:** (+)-epi-α-Bisabolol	**Chemical Name:** 3-Cyclohexene-1-methanol, α,4-dimethyl-α-(4-methyl-3-penten-1-yl)-
CAS Registry Number: 78148-59-1 **Synonyms:** 3-Cyclohexene-1-methanol, α,4-dimethyl-α-(4-methyl-3-penten-1-yl)-, (αR,1S)-; (−)-epi-α-Bisabolol **Molecular Formula:** $C_{15}H_{26}O$ **Molecular Weight:** 222.37 **RIFM Number:** 5184 **Stereochemistry:** Two stereocenters and 4 stereoisomers	**CAS Registry Number:** 76738-75-5 **Synonyms:** 3-Cyclohexene-1-methanol, α,4-dimethyl-α-(4-methyl-3-penten-1-yl)-, (αS,1R)-; (+)-epi-α-Bisabolol **Molecular Formula:** $C_{15}H_{26}O$ **Molecular Weight:** 222.37 **RIFM Number:** 5184 **Stereochemistry:** Two stereocenters and 4 stereoisomers	**CAS Registry Number:** 72691-24-8 **Synonyms:** 3-Cyclohexene-1-methanol, α,4-dimethyl-α-(4-methyl-3-penten-1-yl)- **Molecular Formula:** $C_{15}H_{26}O$ **Molecular Weight:** 222.37 **RIFM Number:** 5184 **Stereochemistry:** Two stereocenters and 4 stereoisomers

2. Physical data

CAS # 515-69-5	CAS # 23089-26-1	CAS # 23178-88-3
Boiling Point: 299.83 °C (EPI Suite) **Flash Point:** Not available **Log K_{OW}:** 5.63 (EPI Suite) **Melting Point**: 55.96 °C (EPI Suite) **Water Solubility:** 1.688 mg/L (EPI Suite) **Specific Gravity:** Not available **Vapor Pressure:** 0.0000746 mm Hg @ 20 °C (EPI Suite v4.0), 0.000136 mm Hg @ 25 °C (EPI Suite) **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$) **Appearance/Organoleptic:** Not available	**Boiling Point:** 299.83 °C (EPI Suite) **Flash Point:** Not available **Log K_{OW}:** 5.63 (EPI Suite) **Melting Point**: 55.96 °C (EPI Suite) **Water Solubility:** 1.688 mg/L (EPI Suite) **Specific Gravity:** Not available **Vapor Pressure:** 0.000136 mm Hg @ 25 °C (EPI Suite) **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$) **Appearance/ Organoleptic:** Not available	**Boiling Point:** Not available **Flash Point:** Not available **Log K_{OW}:** Not available **Melting Point**: Not available **Water Solubility:** Not available **Specific Gravity:** Not available **Vapor Pressure:** Not available **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$) **Appearance/ Organoleptic:** Not available
CAS # 78148–59–1	**CAS # 76738–75–5**	**CAS # 72691–24–8**
Boiling Point: Not available **Flash Point:** Not available **Log K_{OW}:** Not available **Melting Point**: Not available **Water Solubility:** Not available **Specific Gravity:** Not available **Vapor Pressure:** Not available **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$) **Appearance/Organoleptic:** Not available	**Boiling Point:** Not available **Flash Point:** Not available **Log K_{OW}:** Not available **Melting Point**: Not available **Water Solubility:** Not available **Specific Gravity:** Not available **Vapor Pressure:** Not available **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol-1 · cm-1) **Appearance/ Organoleptic:** Not available	**Boiling Point:** Not available **Flash Point:** Not available **Log K_{OW}:** Not available **Melting Point**: Not available **Water Solubility:** Not available **Specific Gravity:** Not available **Vapor Pressure:** Not available **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol-1 · cm-1) **Appearance/ Organoleptic:** Not available

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** < 0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient*** (Creme RIFM Aggregate Exposure Model v2.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.017% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.00008 mg/kg/day or 0.0053 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0014 mg/kg/day (RIFM, 2018)

*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 V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert judgment	Toxtree (v. 2.6)	OECD QSAR Toolbox (v. 3.1)
I*	III	II

*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). See the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

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

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

α-Bisabolol is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):

Ashanti pepper (*Piper guineense* Schum and Thom).
Chamomile.
Citrus fruits.
Eucalyptus oil (*Eucalyptus globulus* Labille).
Hop (*Humulus lupulus*).
Mastic (*Pistacia lentiscus*).
Ocimum species.
Pepper (*Piper nigrum* L.)
Salvia species.
Strawberry (*Fragaria* species).
Tequila (*Agave tequilana*).
Wormwood oil (*Artemisia absinthium*).

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 03/13/19.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for α-bisabolol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.42
2	Products applied to the axillae	0.13
3	Products applied to the face/body using fingertips	2.5
4	Products related to fine fragrances	2.4
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.60
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.60
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.60
5D	Baby cream, oil, talc	0.20
6	Products with oral and lip exposure	1.4
7	Products applied to the hair with some hand contact	3.0
8	Products with significant ano-genital exposure (tampon)	0.20
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.6
10A	Household care products with mostly hand contact (hand dishwashing detergent)	4.6
10B	Aerosol air freshener	17
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.20
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For α-bisabolol, the basis was the reference dose of 2.0 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 5500 μg/cm^2. [b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic potential of α-bisabolol was evaluated in a GLP compliant bacterial reverse mutation test in accordance with OECD TG 471 using the standard plate incorporation method. *S. typhimurium* strains TA1535, TA1537, TA102, TA100, and TA98 were treated with α-bisabolol in dimethyl sulfoxide (DMSO) at concentrations of 0.5, 1.5, 15, 150, and 1500 μg/plate in the presence and absence of metabolic activation (S9 mix) (RIFM, 2002). Further results from an *in vitro* mammalian cell gene mutation test (in accordance with OECD TG 476) found that the target material was unable to induce mutations in the mouse lymphoma thymidine kinase locus assay in the presence and absence of metabolic activation (RIFM, 2008e). α-Bisabolol was considered not mutagenic.

The clastogenic potential of α-bisabolol was assessed in a chromosome aberration study conducted in accordance with OECD TG 473. Chinese hamster V79 cells were exposed to α-bisabolol at concentrations up to 40 μg in the presence of metabolically activated S9 mix and up to 4 μg in the absence of S9 (CIR, 1999). Under the conditions of the study, α-bisabolol was considered not clastogenic.

Taken together, α-bisabolol does not present a concern for genotoxic potential.

Additional References: RIFM, 2008e; Gomes-Carneiro et al., 2005.

Literature Search and Risk Assessment Completed On: 11/15/13.

11.1.2. Repeated dose toxicity

The MOE for α-bisabolol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. The repeated dose toxicity data on α-bisabolol are sufficient for the repeated dose toxicity endpoint. An OECD 410 dermal 28-day subchronic toxicity study in rats determined the NOAEL to be 200 mg/kg/day, based on slight reductions in bodyweight gain and food efficiency as well as transient dermal effects (erythema and diffuse scale formation) (RIFM, 1996). **Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 200/0.0014 or 142857.**

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008d; 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 2.0 mg/kg/day.

The RfD for α-bisabolol was calculated by dividing the NOAEL of 200 mg/kg/day by the uncertainty factor, 100 = 2.0 mg/kg/day.

Additional References: RIFM, 2008b; RIFM, 2008a; CIR, 1999; Kamatou and Viljoen, 2010; ECHA, 2011; RIFM, 2008c; Boutin et al., 1985; Boutin et al., 1981; Meyer and Meyer, 1959; Meyer (1965).bib_Meyer_1965

Literature Search and Risk Assessment Completed On: 11/15/13.

11.1.3. Developmental and Reproductive Toxicity

The MOE is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on α-bisabolol or any read-across materials. The exposure is below the TTC.

11.1.3.1. Risk assessment. The developmental toxicity data on α-bisabolol are sufficient for the developmental toxicity endpoint. Gavage developmental toxicity studies were conducted in rats and rabbits. The developmental NOAEL was determined to be 980 mg/kg/day, based on reduced fetus numbers and increased resorptions in rats (Habersang et al., 1979) and reduced fetus numbers in rabbits (Habersang et al., 1979). These effects were observed at dosages that were maternally toxic. **Therefore, the MOE for developmental toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 980/0.0014 or 700000.**

The reproductive toxicity data on α-bisabolol are insufficient for the reproductive toxicity endpoint. Gavage developmental toxicity studies were conducted in rats and rabbits. The maternal NOAEL was determined to be 980 mg/kg/day, based on clinical signs, food consumption, and body weight in rats (Habersang et al., 1979) and clinical signs and body weight in rabbits (Habersang et al., 1979). There are no male reproductive data on α-bisabolol or any read-across materials that can be used to support the reproductive toxicity endpoints. The total systemic exposure (1.4 μg/kg/day) is below the TTC for α-bisabolol (30 μg/kg bw/day).

Additional References: RIFM, 2008b; RIFM, 2008a; CIR, 1999; Kamatou and Viljoen, 2010; ECHA, 2011; RIFM, 2008c; Boutin et al., 1985; Boutin et al., 1981; Meyer and Meyer, 1959; Meyer (1965).

Literature Search and Risk Assessment Completed On: 11/15/13.

Table 1
Data Summary for α-Bisabolol.

LLNA Weighted Mean EC3 Value (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL μg/cm^2
4593 [2]	Weak	5510[c]	NA	NA	5500

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] Value represents the Maximum Tested No Observed Effect Level (MT-NOEL).

11.1.4. Skin sensitization

Based on the available data, α-bisabolol is considered to be a weak skin sensitizer with a defined NESIL of 5500 μg/cm^2.

11.1.4.1. Risk assessment. Based on the available data, α-bisabolol is considered to be a weak skin sensitizer with a defined NESIL of 5500 μg/cm^2. The weighted mean EC3 value from 2 Local Lymph Node Assays (LLNA) is 4593 μg/cm^2 (RIFM, 1999a; RIFM, 2010a). In a human repeat insult patch test (HRIPT), α-bisabolol did not induce sensitization reactions at 10% or 5510 μg/cm^2 (RIFM, 2010b). The available data demonstrate that α-bisabolol is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 5500 μg/cm^2 (Table 1). Section 10 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. (Api et al., 2008d; 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, https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.ideaproject.info%2Fuploads%2FModules%2FDocuments%2Fqra2-dossier-final–september-2016.pdf&data=02%7C01%7Cs.bhawarlal%40elsevier.com%7C5f31523736bb4c277d6a08d7cb4b64a6%7C9274ee3f94254109a27f9fb15c10675d%7C0%7C0%7C637201397364397263&sdata=f0UekVT4hPlKN1UJh4SDifa%2FE89bDNpdgDT8JoEHjgE%3D&reserved=0) and a reference dose of 2.0 mg/kg/day).

Additional References: RIFM, 1998; RIFM, 1993; RIFM, 1982; RIFM, 1999b.

Literature Search and Risk Assessment Completed On: 07/12/17.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and the available data, α-bisabolol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Additionally, no phototoxic or photoallergic reactions were observed in guinea pigs following topical application of 5% and 0.5% solutions, respectively, and UV irradiation (RIFM, 1977; RIFM, 1983). Based on the lack of significant absorbance and the available *in vivo* data, α-bisabolol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. 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 $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/27/15.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on α-bisabolol. Based on the Creme RIFM Model, the inhalation exposure is 0.0053 mg/day. This exposure is 264.2 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.

Additional References: RIFM, 1980.

Literature Search and Risk Assessment Completed On: 02/11/16.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of α-bisabolol 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, α-bisabolol was not identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did identify α-bisabolol as possibly persistent and 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, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.3. Risk assessment

Based on the current VoU (2015), α-bisabolol does not present a risk to the aquatic compartment in the screening-level assessment.

11.4. Key studies

11.4.1. Biodegradation

For CAS # 515-69-5.

RIFM, 1992**:** The ready biodegradability of the test material was evaluated in the manometric respirometry test according to the OECD 301F method. Under the conditions of this study, biodegradation of 62% was observed after 42 days.

11.4.2. Ecotoxicity

For CAS # 515-69-5.

RIFM, 1990**:** A fish (Golden orfe) acute toxicity study was conducted according to the DIN 38 412 method under static conditions. Under the conditions of the study, the 96-h LC_{50} of the test material was greater than 4.6 mg/L and less than 10 mg/L.

RIFM, 2001**:** A *Daphnia magna* acute immobilization study was conducted according to the OECD 202 method. Under the conditions of the study, the 48-h EC_{50} was reported to be 1.3 mg/L (nominal 6.60 mg/L).

11.5. Other available data

α-Bisabolol has been pre-registered for REACH with no additional data at this time.

Since α-bisabolol passed the screening criteria, measured data is included in the document for completeness only and is not included in the PNEC calculations.

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

Endpoints used to calculate PNEC are highlighted.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.222			1,000,000	0.000222	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.63	5.63
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	< **1**	< **1**

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

The RIFM PNEC is 0.000222 μg/L. The revised PEC/PNECs for EU and NA are not applicable. Therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/04/19.

12. Literature Search*

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

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 01/22/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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. 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 hydrolysed to a common terpene? **No**
Q19. Open chain? **No**
Q23. Aromatic? **No**
Q24. Monocarbocyclic with simple substituents? **Yes**
Q18. Is the substance one of the following (see explanation in Cramer et al., 1978)? **No,** 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.

Boutin, J.A., Lepage, C., Batt, A.M., Siest, G., 1981. The activity of hepatic UDP-glucuronosyltransferase from control and induced pigs toward 17 hydroxylated aglycones. IRCS med. Sci. IRCS Medical Science 9, 633–634.

Boutin, J.A., Thomassin, J., Siest, G., Cartier, A., 1985. Heterogeneity of hepatic microsomal UDP-glucuronosyltransferase activities. Conjugations of phenolic and monoterpenoid aglycons in control and induced rats and Guinea pigs. Biochem. Pharmacol. 34 (13), 2235–2249.

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.

Cosmetic Ingredient Review Expert Panel, 1999. Final report on the safety assessment of bisabolol. Int. J. Toxicol. 18 (Suppl. 3), 33–40.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. In: Food and Cosmetics Toxicology, vol. 16. pp. 255–276 3.

ECHA, 2011. Registration dossier terpineol. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/16031.

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

Gomes-Carneiro, M.R., Dias, D.M.M., De-Oliveira, A.C.A.X., Paumgartten, F.J.R., 2005. Evaluation of mutagenic and antimutagenic activities of alpha bisabolol in the Salmonella/microsome assay. Mutation Research. Genetic Toxicology and Environmental Mutagenesis 585 (1–2), 105–112.

Habersang, S., Leuschner, F., Isaac, O., Thiemer, K., 1979. Pharmacological studies with compounds of chamomile. IV. Studies on toxicity of (-)-alpha-bisabolol. Planta Med. 37, 115–123.

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.

Kamatou, G.P.P., Viljoen, A.M., 2010. A review of the application and pharmacological properties of alpha-bisabolol and alpha-bisabolol-rich oils. J. Am. Oil Chem. Soc. 87 (1), 1–7.

Meyer, F., Meyer, E., 1959. Absorption of ethereal oils and substances contained in them through the skin. Arzneimittel-Forschung [Drug Research]. Arzneim. Forsch. 9, 516–519.

Meyer, F., 1965. Penetrating Agents. Patent. British. 1,001,949, M49750IVa/30h, 7/20/61.

RIFM (Research Institute for Fragrance Materials, Inc), 1977. Alpha-Bisabolol (Dragosantol) (0.5%) Suspension in Peanut Oil): Experimental Investigation on Photo-Sensitizing Effect in guinea Pigs. RIFM, Woodcliff Lake, NJ, USA Unpublished report from Symrise. RIFM report number 60477.

RIFM (Research Institute for Fragrance Materials, Inc), 1980. Acute Toxicity of Alpha-Bisabolol in Rats and Mice. RIFM, Woodcliff Lake, NJ, USA Unpublished report from BASF. RIFM report number 66517.

RIFM (Research Institute for Fragrance Materials, Inc), 1982. Alpha-Bisabolol (Dragosantol): Delayed Contact Hypersensitivity Modified by E.V.Buehler. RIFM, Woodcliff Lake, NJ, USA Unpublished report from Symrise. RIFM report number 60478.

RIFM (Research Institute for Fragrance Materials, Inc), 1983. Alpha-Bisabolol (Dragosantol) 5% in Vaseline: Experimental Investigation on Phototoxic Effect in guinea-pigs. RIFM, Woodcliff Lake, NJ, USA Unpublished report from Symrise. RIFM report number 60480.

RIFM (Research Institute for Fragrance Materials, Inc), 1990. Acute Toxicity of .alpha.-bisabolol in Fish (Golden Orfe). Unpublished Report from BASF. RIFM Report Number 66964. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1992. alpha.-Bisabolol: Biodegradability Unpublished Report from BASF. RIFM Report Number 66966. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1993. Human Patch Test with Alpha-Bisabolol (Dragosantol). RIFM, Woodcliff Lake, NJ, USA Unpublished report from Symrise. RIFM report number 60481.
RIFM (Research Institute for Fragrance Materials, Inc), 1996. Alpha-Bisabolol: Repeated Dose Dermal Toxicity Study in Wistar Rats. RIFM, Woodcliff Lake, NJ, USA Unpublished report from BASF. RIFM report number 66785.
RIFM (Research Institute for Fragrance Materials, Inc), 1998. Alpha-Bisabolol (Dragosantol): Repeated Application Closed Patch Epicutaneous Test under Occlusion. RIFM, Woodcliff Lake, NJ, USA Unpublished report from Symrise. RIFM report number 60483.
RIFM (Research Institute for Fragrance Materials, Inc), 1999. Alpha-Bisabolol (Dragosantol): Local Lymph Node Assay (LLNA) in Mice (Identification of Contact Allergens). RIFM, Woodcliff Lake, NJ, USA Unpublished report from Symrise. RIFM report number 60485.
RIFM (Research Institute for Fragrance Materials, Inc), 1999. Alpha-Bisabolol (Dragosantol): Buehler Delayed Contact Hypersensitivity Study in the guinea Pig. RIFM, Woodcliff Lake, NJ, USA Unpublished report from Symrise. RIFM report number 60484.
RIFM (Research Institute for Fragrance Materials, Inc), 2001. alpha.-Bisabolol (Bisabolol Nat. Roh (Candela-Öl)): Acute Effect on Daphnia Magna STRAUS. RIFM, Woodcliff Lake, NJ, USA Unpublished report from BASF. RIFM report number 66967.
RIFM (Research Institute for Fragrance Materials, Inc), 2002. Mutagenicity Study of Alpha-Bisabolol (Dragosantol) in the Salmonella typhimurium/mammalian Microsome Reverse Mutation Assay (Ames-Test). RIFM, Woodcliff Lake, NJ, USA Unpublished report from Symrise. RIFM report number 60486.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. A Toxicologic and Dermatologic Assessment of Cyclic and Non-cyclic Terpene Alcohols when Used as Fragrance Ingredients. RIFM Report Number 56372. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. Fragrance Material Review on Alpha-Bisabolol. RIFM Report Number 56377. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. Fragrance Material Review on Terpineol. RIFM Report Number 56408. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. 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), 2008. Cell Mutation Assay at the Thymidine Kinase Locus (TK+/-) in Mouse Lymphoma L5178Y Cells with Alpha-Bisabolol (Dragosantol). RIFM, Woodcliff Lake, NJ, USA Unpublished report from Symrise. RIFM report number 60487.
RIFM (Research Institute for Fragrance Materials, Inc), 2010. Alpha-Bisabolol (Dragosantol 100): Local Lymph Node Assay (LLNA) in Mice to Identify Contact Allergens. RIFM, Woodcliff Lake, NJ, USA Unpublished report from Symrise. RIFM report number 60488.
RIFM (Research Institute for Fragrance Materials, Inc), 2010. Repeated Insult Patch Test with .alpha.-bisabolol. Unpublished Report from Symrise. RIFM Report Number 63084. RIFM, Woodcliff Lake, NJ, USA.
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.