Food and Chemical Toxicology 110 (2017) S309–S317

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment, 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol, CAS Registry Number 72089-08-8

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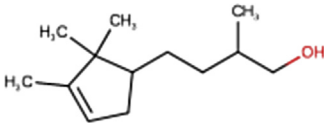
ARTICLE INFO

Article history:
Received 8 May 2017
Received in revised form
30 May 2017
Accepted 3 June 2017
Available online 6 June 2017

Version: 041917. This version replaces any previous versions.
Name: 2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol
CAS Registry Number: 72089-08-8



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Abbreviation 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; Safford et al., 2015; Safford 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
EU - Europe/European Union
GLP - Good Laboratory Practice

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http://dx.doi.org/10.1016/j.fct.2017.06.001
0278-6915/

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IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
TTC - Threshold of Toxicological Concern
UV/Vis Spectra - Ultra Violet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WOE - Weight of Evidence

1. Identification

1 **Chemical Name**: 2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl) butanol
2 **CAS Registry Number**: 72089-08-8
3 **Synonyms**: Brahmanol; 3-Cyclopentene-1-butanol,.β.,2,2,3-tetramethyl-; 2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl) butanol; b,2,2,3-Tetramethylcyclopent-3-ene-1-butanol; Methyl-(trimethyl cyclo-pentenyl)-butanol
4 **Molecular Formula**: $C_{13}H_{24}O$
5 **Molecular Weight**: 196.33
6 **RIFM Number**: 1182

2. Physical data

1 **Boiling Point**: 257.14 °C [EPI Suite], 265–271 °C at 1013 hPa [RIFM, 2016a]
2 **Flash Point**: >212 °F [RIFM database 230 °F [RIFM database], 128.0 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) [RIFM, 2016b]
3 **Log KOW**: 4.66 [EPI Suite]
4 **Melting Point**: 37.13 °C [EPI Suite], −67 °C at 1013 hPa [RIFM, 2016a]
5 **Water Solubility**: 15.55 mg/L [EPI Suite]

The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two -digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (*i.e.*, SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, *etc*. A key study for each endpoint was selected based on the most conservative end-point value (*e.g.*, PNEC, NOAEL, LOEL, and NESIL).
*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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data on the read across analog 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) show that this material is not genotoxic and it is not a concern for skin sensitization. The MOE >100 for the repeated dose, developmental and reproductive toxicity endpoints is acceptable. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoints were evaluated and the material was not found to be a PBT; its risk quotients, based on current volume of use in Europe and North America, were acceptable (PEC/PNEC < 1).

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 2007a; RIFM, 2014a,b,c)
Repeated Dose Toxicity: NOAEL = 300 mg/kg/day (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol)
Developmental and Reproductive Toxicity: NOAEL = 750 mg/kg/day and 300 mg/kg/day, respectively. (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol)
Skin Sensitization: Not sensitizing (RIFM, 1983a; RIFM, 1978; RIFM, 1985a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB; RIFM, 1983b; RIFM, 1983c)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 36.3% (BODIS) (RIFM, 1995)
Bioaccumulation: Screening Level: 550 L/kg (Epi Suite v4.1)
Ecotoxicity: Screening Level: 48 h *Daphnia magna* EC50: 0.48 mg/L (Epi Suite v4.1)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-Level: PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 0.48 mg/L (Epi Suite ver 4.1)
RIFM PNEC is: 0.048 μg/L

- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1

6 **Specific Gravity**: 0.8987–0.9047 (25 °C) [RIFM database], 0.8950-0.9090-0.9090 [RIFM], 0.900–0.906 (20/4 °C) [RIFM database]
7 **Vapor Pressure**: 0.00158 mm Hg @ 25 °C [EPI Suite], 0.000818 mmHg @ 20 °C [EPI Suite 4.0]
8 **UV Spectra**: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol-1 · cm-1)
9 **Appearance/Organoleptic**: A clear, colorless to pale yellow liquid with a mild sandalwood note.

3. Exposure

1 **Volume of Use (worldwide band)**: 1–10 metric tons per year (IFRA, 2011)
2 **95**th **Percentile Concentration in Hydroalcoholics**: 0.056% (RIFM, 2014c)
3 **Inhalation Exposure***: 0.00024 mg/kg/day or 0.019 mg/day (RIFM, 2014c)
4 **Total Systemic Exposure****: 0.0020 mg/kg/day (RIFM, 2014c)

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2 **Analogs Selected**:
a **Genotoxicity**: 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6)
b **Repeated Dose Toxicity**: 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6)
c **Reproductive Toxicity**: 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6)
d **Skin Sensitization**: None
e **Phototoxicity/Photoallergenicity**: None
f **Local Respiratory Toxicity**: None
g **Environmental Toxicity**: None
3 **Read-across Justification**: See Appendix below

6. Metabolism

Not considered for this risk assessment.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol 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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 04/20/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol does not present a concern for genotoxicity.

10.1.2. Risk assessment

2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol was assessed in the BlueScreen assay and found negative for genotoxicity with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol however, read across can be made to 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section 5). The mutagenicity of read across material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* strain WP2uvrA were treated with 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2007a). These results indicate that 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol is non-mutagenic in the Ames test when tested up to 5000 μg/plate under the conditions of the study.

There are no studies assessing the clastogenic activity of 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol however, read across can be made to 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section 5). The clastogenicity of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung fibroblasts were treated with 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol in DMSO at concentrations up to 190 μg/mL in the presence and

absence of exogenous metabolically active microsomal mixture. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, either with or without metabolic activation (RIFM, 2014a). Under the conditions of the study, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the available data 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol does not present a concern for genotoxic potential and this can be extended to 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol.

Additional References: RIFM, 1985b; RIFM, 1998; RIFM, 1990; RIFM, 1987; RIFM, 2007b.

Literature Search and Risk Assessment Completed on: 01/10/2016.

10.1.3. Repeated dose toxicity

The margin of exposure for 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no repeated dose toxicity data on 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol. Read across material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section 5) have sufficient repeated dose toxicity data. A 28-day repeated-dose oral toxicity study was conducted with test material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (bacdanol). Groups of 5 Crl:CD(SD) rats/sex/dose were administered via gavage test material at dose levels of 0, 100, 350 and 1000 mg/kg/day dissolved in corn oil for 28 days. Control and high dose recovery groups were set for the control and 1000 mg/kg/day groups to investigate reversibility of the effect of the treatment for 14 days. Effects on the liver and kidneys and irritating effects on the digestive tracts, such as the forestomach, attributable to the test substance were detected but only at the highest dose tested. Microscopic alterations included, test material related alterations in the hepatocytes and kidney tubules as well as the stomach. All these effects were seen to be reversible, except for incidences of granulomas of the female hepatocytes. Hence, the NOAEL was determined to be 350 mg/kg/day (RIFM, 2014b).

In another OECD 422 GLP study conducted with test material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol, there were 3 treatment groups. Treatment groups were: the Toxicity subgroup (Toxicity phase), 10 males and 5 females/dose (except for control males and at top dose: 5 males/dose), the Reproductive subgroup (Main Phase), 10 females/dose and same males as for toxicity subgroup and the Recovery subgroup, 5 males and 5 females/dose (control and top dose). Recovery phase males were also used for pairing with Main reproductive phase females. The animals received test material at doses of 0, 100, 300 or 1000 mg/kg/day in corn oil. Mortality was reported among the high dose group females and typical terminal clinical signs were reported among these females. Lower food consumption and body weight gains were reported among high dose group females. Kidney and liver weights were increased among high dose females. No such effects persisted among the recovery group animals. Microscopic findings included, centrilobular hepatocytes enlargement among females. These effects were not observed among the recovery group animals. No adverse effects were reported among the low and mid dose group animals. Thus, the NOAEL for the male and female systemic toxicity was determined to be 300 mg/kg/day due to mortality and clinical conditions reported among high dose females (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol). In another study, test material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol was administered to 10 Crl:CD(SD) rats/sex/dose at doses of 0, 1500, 5000 or 15 000 ppm (equivalent to 100, 330 and 981 mg/kg/day for males and 109, 362 and 1109 mg/kg/day for females, respectively according to body weight and food consumption parameters). An additional group of 5 male and 5 female rats were assigned to the control and high dose groups. The study was conducted according to the OECD 408 protocol. Reduced food consumption, with associated reductions in body weight gain was evident in the 15 000 ppm group however, this was attributed to the treated diet being unpalatable due to the high concentration of test material, but not adverse effect due to treatment with test material. Alterations in hematological parameters were reported but were not considered to be due to treatment with test material. Organ weight analysis indicated dose-dependent and statistically significantly higher than control body weight-adjusted liver weight in all groups of treated males and in females administered 5000 or 15 000 ppm of test material. Relative kidney weights were higher than control in females given 15 000 ppm, and body weight-adjusted uterus and cervix weights were slightly low in females given 5000 or 15 000 ppm. Following 4 weeks of recovery, relative liver weights in males previously given 15 000 ppm remained slightly higher than control, although the magnitude of the difference was lower than that recorded at the end of the treatment period. Plasma biochemistry revealed several slight changes in composition which were indicative of adaptations of metabolism/excretion in the liver and kidneys, and were accompanied by increases in liver and kidney weight. Under the conditions of this study, there was clear evidence of systemic exposure but no effects were deemed to be adverse. Thus, the NOAEL was determined to be 15 000 ppm, equivalent to 981 mg/kg/day for males and 1109 mg/kg/day for females the highest dose tested (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol). The most conservative NOAEL of 300 mg/kg/day from the 28-day study was selected for the repeated dose toxicity endpoint. Since there is a 13-week dietary study on the same chemical indicating a higher NOAEL, the safety factor was not included to derive a NOAEL from the 28-day study. Therefore, the 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol NOAEL in mg/kg/day by the total systemic exposure to 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol, 300/0.002 or 150 000.

In addition, the total systemic exposure to 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol (2 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2000.

Literature Search and Risk Assessment Completed on: 10/18/2016.

10.1.4. Developmental and reproductive toxicity

The margin of exposure for 2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol is adequate for the developmental and reproductive toxicity endpoint at the current level of use.

10.1.4.1. Risk assessment. There are no developmental toxicity data on 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol. Read across material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section 5) has sufficient developmental toxicity data. An OECD 414 GLP prenatal developmental toxicity study was conducted with test material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol.
Groups of mated female Crl:CD(SD) rats (20/dose) were gavaged with test material at dose levels of 0, 100, 300 and 750 mg/kg/day in corn oil from days 6–19 after mating. Maternal weight gain

during gestation and uterine weights were lower as compared to controls. The mean fetal weights were lower than the controls for the 300 and 750 mg/kg/day dose groups. This was considered to be due to maternal toxicity and not considered to be a developmental toxicity adverse effect. Incidences of skeletal variations and ossifications were observed among the pups of the treated animals however, this was again considered to be due to maternal toxicity and not considered to be an adverse developmental toxic effect due to test material administration. Thus, the NOAEL for developmental toxicity was determined to be 750 mg/kg/day, the highest dose tested (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol). Therefore, the 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol MOE for the developmental toxicity endpoint can be calculated by dividing the 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol NOAEL in mg/kg/day by the total systemic exposure to 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol, 750/0.002 mg/kg/day or 375 000.

There are no reproductive toxicity data on 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol. Read across material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section 5) have sufficient reproductive toxicity data. An OECD 422 GLP study was conducted with test material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol. There were 3 treatment groups: the Toxicity subgroup (Toxicity phase), 10 males and 5 females/dose (except for control males and at top dose: 5 males/dose), the Reproductive subgroup (Main Phase), 10 females/dose and same males as for toxicity subgroup and the Recovery subgroup, 5 males and 5 females/dose (control and top dose). Recovery phase males were also used for pairing with Main reproductive phase females. There were no adverse effects towards the male and female reproductive organs up to the highest dose tested. However, mortality was reported among animals of the high dose group. Thus, the NOAEL for the reproductive toxicity endpoint was considered to be 300 mg/kg/day, the highest dose tested (ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol). Therefore, the 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl) butanol MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol NOAEL in mg/kg/day by the total systemic exposure to 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol, 1000/0.002 mg/kg/day or 150 000.

In addition, the total systemic exposure to 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol (2 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2000.

Literature Search and Risk Assessment Completed on: 10/18/2016.

10.1.5. Skin sensitization

Based on the existing data, 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol does not present a concern for skin sensitization.

10.1.5.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In guinea pig sensitization tests, 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol was found to be a non-sensitizer (RIFM, 1983a,b,c; RIFM, 1978). Moreover, in a confirmatory human maximization test, no positive reactions were observed at 10% or 6900 μg/cm^2 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol in petrolatum (RIFM, 1985a). Based on weight of evidence from structural analysis, animal and human studies, 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/19/2015.

10.1.6. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available *in vivo* experimental study data, 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.6.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L·mol^{-1} · cm^{-1} (Henry et al., 2009). In studies conducted to assess the phototoxic and photoallergenic potential of 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol in guinea pigs, 10% test material was not phototoxic (RIFM, 1983a) and 20% test material was not photoallergenic (RIFM, 1983b). Based on lack of absorbance and *in vivo* experimental study data, 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol would not be expected to present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/04/16.

10.1.7. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.7.1. Risk assessment. There are no inhalation data available on 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol. Based on the Creme RIFM model, the inhalation exposure is 0.019 mg/day. This exposure is 73.7 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: None.

Literature Search and Risk Assessment Completed on: 10/20/2016.

11. Environmental endpoint summary

11.1. Screening-level assessment

A screening level risk assessment of 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety

Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (*e.g.*, OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (*e.g.*, USEPA's BIOWIN and BCFBAF found in EPI SUITE v4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2. Risk assessment

Based on the current Volume of Use (2011), 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol presents a risk to the aquatic compartment in the screening level assessment.

11.2.1. Biodegradation

RIFM, 1995: The biodegradability of the test material was evaluated using the BOD test for insoluble substances (BODIS). Degradation determined by measuring oxygen consumption in a closed vessel over 28 day and was 36.3%.

11.2.2. Ecotoxicity

No data available.

11.2.3. Other available data

2 -Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol has been pre-registered for REACH with no additional data at this time.

12. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.66	4.6
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
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 0.048 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 7/8/2015.

Literature search*

- **RIFM database**: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA**: http://echa.europa.eu/
- **NTP**: http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder**: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED**: http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET**: http://toxnet.nlm.nih.gov/
- **IARC**: (http://monographs.iarc.fr)
- **OECD SIDS**: http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor**: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS**: http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary**: http://cfpub.epa.gov/hpv-s/
- **Japanese NITE**: http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base**: http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google**: https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	1.285 mg/L			1,000,000	0.001285 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** Ver 1.11	0.661 mg/L	0.480 mg/L	0.986 mg/L	10,000	0.0480 μg/L	Neutral Organic

as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.06.001.

Transparency document

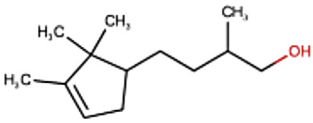
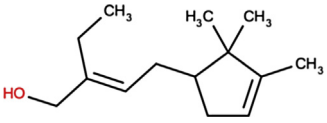
Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.06.001.

Appendix

Read across justification

Methods:

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- The Jmax were calculated using RIFM skin absorption model (SAM)the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target material	Read across material
Principal Name	2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol	2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol
CAS No.	72089-08-8	28219-61-6
Structure		
Similarity (Tanimoto score)[1]		0.825
Read across endpoint		• Developmental and Reproductive • Genotoxicity • Repeated dose
Molecular Formula	$C_{13}H_{24}O$	$C_{14}H_{24}O$
Molecular Weight	196.33	208.35
Melting Point (°C, EPISUITE)	37.13	60.19
Boiling Point (°C, EPISUITE)	257.14	298.07
Vapor Pressure (Pa @ 25°C, EPISUITE)	0.21	0.00958
Log Kow (KOWWIN v1.68 in EPISUITE)	4.66	4.4[1]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	15.55	5.256
J_{max} (mg/cm^2/h, SAM)	24.773	10.985
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	3.69E-005	5.09E-005
Genotoxicity		
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• arcinogen (low reliability)	• Non carcinogen (moderate reliability)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
In-vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found
In-vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	• Non binder without OH or NH_2 group	• Non binder without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• toxicant (low reliability)	• toxicant (low reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

1. RIFM, 2004.

Summary

There are insufficient toxicity data on 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol (CAS # 72089-08-8). Hence *in-silico* evaluation was conducted by determining suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analog 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) was identified as a proper read across material with data for its respective toxicity endpoints.

Conclusion/Rationale

- 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) could be used as structurally similar read across analog for target material 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol (CAS # 72089-08-8) for the genotoxicity, reproductive and developmental toxicity, and repeated dose toxicity endpoints.
  - o The target substance and the read across analog are structurally similar and belong to a class of unsaturated cyclic terpene alcohols.
  - o The target and read across material have the (2,2,3-trimethyl-3-cyclopentenyl)butanol substructure common among them.
  - o The key difference between the target substance and the read across analog is that the read across analog has an additional vinylene group in the aliphatic chain which the target lacks.
  - o The target substance and the read across analog have a Tanimoto score as mentioned in the above table. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxicological perspective.
  - o The target substance and the read across analog have similar physical chemical properties. Any differences in some of the physical chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for genotoxicity, reproductive and developmental toxicity, and repeated dose toxicity endpoints are consistent between the target substance and the read across analog.
  - o According to CAESAR model, both the read across analog and the target substance are predicted to be toxicants for developmental toxicity endpoint. The data described in the developmental toxicity section above describes that the read across substance pose no concern. Therefore, the alert will be superseded by the availability of data.
  - o According to ISS model, only the target substance is predicted to be a carcinogen for the genotoxicity endpoint. All other genotoxicity alerts for the target substance and the read across analogs are negative. The data described in the genotoxicity section shows that the read across analogs pose no concern for the genotoxicity endpoint. Based on a comparison of structure similarity, physical-chemical properties and reactivity predictions between the read across analogs and the target substance, the alert for the target was superseded by the availability of data for the read across analogs.
  - o The target substance and the read across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for genotoxicity, reproductive and developmental toxicity, and repeated dose toxicity endpoints are consistent between the metabolites of the read across analog and the target substance.
  - o The structural differences between the target substance and the read across analog are deemed to be toxicologically insignificant for genetoxicity, reproductive and developmental toxicity, and repeated dose toxicity endpoints.

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., Renkers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the research institute for fragrance materials, inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

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

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

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

ECHA Dossier: 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol: https://echa.europa.eu/, Accessed 4/21/2017.

Epi Suite, 2011. Essential estimation programs interface SuiteTM (version 4.1) [software]. (Copyright 2000-2011). U. S. Environ. Prot. Agency's Off. Pollut. Prev. Toxics Syracuse Res. Corp. 20 (6), 482–487. Retrieved from: http://www.epa.gov/opptintr/exposure/pubs/episuite.htm. Research.

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), 2011. Volume of Use Survey, February 2011.

OECD, 2012. OECD QSAR Toolbox 3 (1). http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc), 1978. The Delayed Contact Sensitization Test of 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol (Brahmanol) in Guinea Pigs. Unpublished report from Dragoco Inc. RIFM report number 1921 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 1983a. Experimental Investigation of 2-methyl-4(2,2,3-trimethyl-3-cyclopentyl)butanol (Brahmanol) on Phototoxic Effect in Guinea Pigs. Unpublished report from Dragoco Gerberding & Co. RIFM report number 31388 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 1983b. 2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol (Brahmanol) 20% in Vaseline: Delayed Contact Hypersensitivity in Guinea-pigs Modified by Magnusson and Kligman. Unpublished report from Dragoco Gerberding and Co. GmbH. RIFM report number 37844 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 1983c. 2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol (Brahmanol) 20% in Vaseline: Experimental Investigation on Photosensitizing Effect in Guinea-pigs Modified by Vinson & Borselli. Unpublished report from Dragoco Gerberding and Co. GmbH. RIFM report number 37845 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 1985a. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1919 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 1985b. Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol. Unpublished report from International Flavors and Fragrances. RIFM report number 19968 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 1987. The Effect of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol in a Bacterial Mutation Assay. Unpublished report from Quest International. RIFM report number 49856 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 1990. *In Vitro* Cytogenetics Study of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol. Unpublished report from Quest International. RIFM report number 49855 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 1995. Assessment of the Biodegradability of 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol (Brahmanol) with the BOD Test for Insoluble Substances (BODIS). Unpublished report from Symrise. RIFM report number 58349 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 1998. Bacterial Reverse Mutation Test "Ames Test" of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (Levosandol). Unpublished report from Takasago International Corporation. RIFM report number 33070 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 2000. Monographs on Fragrance Raw Materials. RIFM report number 60814 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc), 2004. Partition Coefficient N-octanol/water of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol

(Radjanol Super). Unpublished report from Givaudan. RIFM report number 55882 (RIFM, Woodcliff Lake, NJ, USA.).
RIFM (Research Institute for Fragrance Materials, Inc), 2007a. 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (Bangalol): Reverse Mutation Assay "Ames Test" Using *Salmonella typhimurium* and Escherichia coli. Unpublished report from Givaudan. RIFM report number 54235 (RIFM, Woodcliff Lake, NJ, USA.).
RIFM (Research Institute for Fragrance Materials, Inc), 2007b. Mutagenicity Test of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (Bacdanol) Using Microorganisms. Unpublished report from International Flavors and Fragrances. RIFM report number 54272 (RIFM, Woodcliff Lake, NJ, USA.).
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of 2-methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65696 (RIFM, Woodcliff Lake, NJ, USA.).
RIFM (Research Institute for Fragrance Materials, Inc), 2014a. Chromosomal Aberration Test of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (Bacdanol) Using Cultured Mammalian Cells. Unpublished report from International Flavors & Fragrances Inc. RIFM report number 69572 (RIFM, Woodcliff Lake, NJ, USA.).
RIFM (Research Institute for Fragrance Materials, Inc), 2014b. Twenty-eight-day Repeated-dose Oral Toxicity Study of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (Bacdanol) in Rats. Unpublished report from International Flavors & Fragrances Inc. RIFM report number 69574 (RIFM, Woodcliff Lake, NJ, USA.).
RIFM (Research Institute for Fragrance Materials), 2014c. Use Level Survey. April 2014.
RIFM (Research Institute for Fragrance Materials, Inc), 2016a. 2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol (Brahmanol): Determination of Physicochemical Properties Melting Point and Boiling Point. Unpublished report from RIFM report number 71151 (RIFM, Woodcliff Lake, NJ, USA.).
RIFM (Research Institute for Fragrance Materials, Inc), 2016b. 2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol (Brahmanol): Determination of Physicochemical Properties Flash Point. Unpublished report from RIFM report number 71164 (RIFM, Woodcliff Lake, NJ, USA.).
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., 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.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.
USEPA, 2012. Estimation Programs Interface Suite™.