



RIFM fragrance ingredient safety assessment, β -caryophyllene, CAS Registry Number 87-44-5

A.M. Api^a, D. Belsito^b, 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, L. Jones^a, K. Joshi^a, M. Kumar^a, A. Lapczynski^a, M. Lavelle^a, I. Lee^a, D.C. Lieblerⁱ, H. Moustakas^a, M. Na^a, T.M. Penning^j, G. Ritacco^a, J. Romine^a, N. Sadekar^a, T.W. Schultz^k, D. Selechnik^a, F. Siddiqi^a, I.G. Sipes^l, G. Sullivan^{a,*}, Y. Thakkar^a, Y. Tokura^m

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

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

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

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

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

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

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

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

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

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

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

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

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

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ABSTRACT

The existing information supports the use of this material as described in this safety assessment. β -Caryophyllene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that β -caryophyllene is not genotoxic. Data on β -caryophyllene provided a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and fertility endpoints. The developmental and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to β -caryophyllene is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data show that there are no safety concerns for β -caryophyllene for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; β -caryophyllene is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; β -caryophyllene 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.

* Corresponding author.

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

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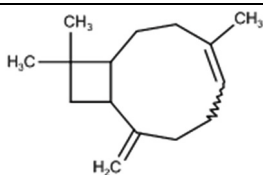
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Name: β -Caryophyllene CAS Registry Number: 87-44-5



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

CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)

Crema RIFM Model - The Crema 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

DRF - Dose Range Finding

DST - Dermal Sensitization Threshold

ECHA - European Chemicals Agency

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

EU - Europe/European Union

GLP - Good Laboratory Practice

IFRA - The International Fragrance Association

LOEL - Lowest Observed 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

Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.

QRA - Quantitative Risk Assessment

QSAR - Quantitative Structure-Activity Relationship

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

RfD - Reference Dose

RIFM - Research Institute for Fragrance Materials

RQ - Risk Quotient

Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test

TTC - Threshold of Toxicological Concern

UV/Vis spectra - Ultraviolet/Visible spectra

VCF - Volatile Compounds in Food

VoU - Volume of Use

vPvB - (very) Persistent, (very) Bioaccumulative

WoE - Weight of Evidence

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

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

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

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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.

β -Caryophyllene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that β -caryophyllene is not genotoxic. Data on β -caryophyllene provided a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and fertility endpoints. The developmental and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to β -caryophyllene is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data show that there are no safety concerns for β -caryophyllene for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; β -caryophyllene is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; β -caryophyllene 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, 1984; Molina-Jasso et al., 2009)

Repeated Dose Toxicity: NOAEL = 1033 mg/kg/day. RIFM (2013)

Reproductive Toxicity: Developmental toxicity: No NOAEL available. Exposure is below the TTC. Fertility: NOAEL = 1367 mg/kg/day. RIFM (2013)

Skin Sensitization: No concern for skin sensitization under the current, declared levels of use. RIFM (2016)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 2020)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 70% (OECD 301F) RIFM (2007)

Bioaccumulation: Screening-level: 6682 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 4.6 mg/L RIFM (2001a)

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: 48-h *Daphnia magna* EC50: 4.6 mg/L RIFM (2001a)

RIFM PNEC is: 0.92 μ g/L

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

1. Identification

- Chemical Name:** β -Caryophyllene
- CAS Registry Number:** 87-44-5
- Synonyms:** Bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene-, [1R-(1R*,4E,9S*)]-; Caryophyllene; 2-Methylene-6,10,10-trimethylbicyclo[7.2.0]undecene-5-ene; 加力代烯; 4,11,11-Trimethyl-8-methylenebicyclo[7.2.0]undec-4-ene; Caryophyllene Nat. Rect.; β -Caryophyllene
- Molecular Formula:** $C_{15}H_{24}$
- Molecular Weight:** 204.35
- RIFM Number:** 236

7. **Stereochemistry:** Isomer not specified. One stereocenter and 2 chiral centers present. Two stereoisomers and 4 enantiomers possible.

2. Physical data

1. **Boiling Point:** 260 °C (Fragrance Materials Association [FMA]), 260.0 °C (1013.0 mbar) (RIFM, 2002b), 256.8 °C (EPI Suite), 253–262 °C (corrected to normal atmospheric pressure of 1013 hPa) (RIFM, 2017d)
2. **Flash Point:** >200 °F; CC (FMA), >93 °C (Globally Harmonized System), 105.5 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2017e)
3. **Log Kow:** 6.3 (EPI Suite), 6.23 ± 0.15 at 25 ± 1 °C (RIFM, 2017c)
4. **Melting Point:** 43.42 °C (EPI Suite), no melting point down to –100 °C (at atmospheric pressure of 1021 hPa) (RIFM, 2017d)
5. **Water Solubility:** 0.05011 mg/L (EPI Suite)
6. **Specific Gravity:** 0.910 (FMA)
7. **Vapor Pressure:** 0.02 mm Hg at 20 °C (EPI Suite v4.0), 0.007 mm Hg at 20 °C (FMA), 0.0312 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark ($1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$)
9. **Appearance/Organoleptic:** A colorless oily liquid that has a woody-spicy, dry, and tenacious odor. Many descriptions include "clove-like."

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient

1. **95th Percentile Concentration in Fine Fragrance:** 0.042% (RIFM, 2017a)
2. **Inhalation Exposure*:** 0.00017 mg/kg/day or 0.012 mg/day (RIFM, 2017a)
3. **Total Systemic Exposure**:** 0.0014 mg/kg/day (RIFM, 2017a)

*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).

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	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:

- a. **Genotoxicity:** None
- b. **Repeated Dose Toxicity:** None
- c. **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

No relevant data available for inclusion in this safety assessment.

Additional References: None.

8. Natural occurrence

β -Caryophyllene is reported to occur in the following foods by the VCF*:

Cloves (*Eugenia caryophyllata* Thunberg).
 Curry (*Bergera koenigii* L.)
 Hop (*Humulus lupulus*).
 Lemon balm (*Melissa officinalis* L.)
 Mastic (*Pistacia lentiscus*).
 Mentha oils.
 Ocimum species.
 Pepper (*Piper nigrum* L.)
 Pistacia atlantica.
 Salvia species.

*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. This is a partial list.

9. REACH dossier

Available; accessed 09/28/20.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, β -caryophyllene does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of β -caryophyllene has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent with OECD TG 471. Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with β -caryophyllene in ethanol at concentrations up to 150 $\mu\text{L}/\text{plate}$. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 1984). Under the conditions of the study, β -caryophyllene was not mutagenic in the Ames test.

The clastogenic activity of β -caryophyllene was evaluated in an in vivo micronucleus test. The test material was administered in corn oil orally to groups of male and female NIH mice. Doses of 20, 200, or 2000

mg/kg body weight were administered. Mice from each dose level were euthanized at 24, 48, 72, and 96 h; the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (Mollina-Jasso et al., 2009). Under the conditions of the study, β -caryophyllene was considered to be not clastogenic in the in vivo micronucleus test.

Based on the data available, β -caryophyllene does not present a concern for genotoxic potential.

Additional References: Heck et al., 1989; Sasaki et al., 1989; DiSotto et al., 2008.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on β -caryophyllene to support the repeated dose toxicity endpoint. An OECD 408/GLP dietary 90-day subchronic toxicity study was conducted in Sprague Dawley rats. Groups of 10 male rats/dose were fed diets containing 0, 3500, 7000, or 21000 ppm β -caryophyllene (calculated average daily intake of 0, 222, 456, or 1367 mg/kg/day, respectively) for 90 days. Groups of 10 female rats/dose were fed diets containing 0, 3500, 14000, or 56000 ppm β -caryophyllene (calculated average daily intake of 0, 263, 1033, or 4278 mg/kg/day, respectively) for 90 days. There was a statistically significant increase in the relative kidney weights in males treated with 21000 ppm test material. Macroscopic findings revealed enlarged kidneys in a single high-dose male rat. This macroscopic finding may be related to the increased kidney weights and the observed microscopic findings of nephropathy and tubular cytoplasmic droplets in the male kidneys among all treated groups. These kidney alterations in males were confirmed with Mallory-Heidenhain staining and were consistent with documented changes of alpha-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990). There was a statistically significant increase in the relative liver weights among males and females of the mid and high-dose groups, which corresponded to histopathological findings of hepatocellular hypertrophy with a dose-response. The relative liver weight increases were as follows: 116% for mid-dose males, 135% for high-dose males, 131% for mid-dose females, and 194% for high-dose females. Liver weight increases below 150% can be considered to be adaptive provided there is a lack of histopathological evidence of necrosis, fibrosis, inflammation, and steatotic vacuolar degeneration showing liver cell damage and clinical chemistry alterations (Hall et al., 2012). Therefore, the relative liver weight increase in high-dose females was considered to be adverse even though there was no evidence of vacuolar degeneration of the liver. Minimal to slight erythrocytes within the sinuses of mesenteric lymph nodes were also observed in the mid- and high-dose animals; however, only high-dose males exhibited a statistically significant reduction in the absolute spleen weight with no treatment-related hematological alterations. Thus, the systemic toxicity NOAEL for males was considered to be 21000 ppm or 1367 mg/kg/day, the highest dose tested. The NOAEL for females was considered to be 14000 ppm or 1033 mg/kg/day, based on the adverse liver weight increases at the highest dose group (RIFM, 2013). The most conservative NOAEL of 1033 mg/kg/day was

considered for the repeated dose toxicity endpoint. Therefore, the β -caryophyllene MOE can be calculated by dividing the β -caryophyllene NOAEL in mg/kg/day by the total systemic exposure to β -caryophyllene, 1033/0.0014, or 737857.

In addition, the total systemic exposure to β -caryophyllene (1.4 μ g/kg/day) is below the TTC (30 μ g/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/12/20.

11.1.3. Reproductive toxicity

There are insufficient developmental toxicity data on β -caryophyllene or any read-across materials. The total systemic exposure to β -caryophyllene is below the TTC for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

The MOE for β -caryophyllene is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental data on β -caryophyllene or any read-across material that can be used to support the developmental toxicity endpoint. The total systemic exposure to β -caryophyllene (1.4 μ g/kg/day) is below the TTC (30 μ g/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are sufficient reproductive data on β -caryophyllene to support the reproductive toxicity endpoint. An OECD 408/GLP dietary 90-day subchronic toxicity study was conducted in Sprague Dawley rats. Groups of 10 male rats/dose were fed diets containing 0, 3500, 7000, or 21000 ppm β -caryophyllene (calculated average daily intake of 0, 222, 456, or 1367 mg/kg/day, respectively) for 90 days. Groups of 10 female rats/dose were fed diets containing 0, 3500, 14000, or 56000 ppm β -caryophyllene (calculated average daily intake of 0, 263, 1033, or 4278 mg/kg/day, respectively) for 90 days. In addition to the systemic toxicity parameters, the male and female reproductive organs were also assessed. There were no treatment-related effects observed on estrous cycling, sperm analysis, or reproductive organ weights and histopathology up to the highest dose tested. The NOAEL for reproductive toxicity was considered to be 21000 ppm (1367 mg/kg/day) and 56000 ppm (4278 mg/kg/day) for males and females, respectively (RIFM, 2013; RIFM, 2014). The most conservative NOAEL of 1367 mg/kg/day was selected for the reproductive toxicity endpoint. Therefore, the β -caryophyllene MOE can be calculated by dividing the β -caryophyllene NOAEL in mg/kg/day by the total systemic exposure to β -caryophyllene, 1367/0.0014, or 976429.

In addition, the total systemic exposure to β -caryophyllene (1.4 μ g/kg/day) is below the TTC (30 μ g/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.4. Skin sensitization

Based on the existing data, β -caryophyllene presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, β -caryophyllene is not considered a skin sensitizer. Limited studies indicate a sensitization

potential from the degradation products of β -caryophyllene by autoxidation. This assessment is consistent with data on other terpene compounds, which include similar unsaturated substructures, demonstrating that the pure material is not sensitizing, whereas autoxidation products are known to be contact allergens (i.e., linalool CAS # 78-70-6). The chemical structure of β -caryophyllene indicates that it would not have the potential to act as a skin sensitizer directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2)*. A carefully controlled series of experiments in guinea pigs have demonstrated that β -caryophyllene oxide (reportedly a major autoxidation product) is sensitizing, but β -caryophyllene is not sensitizing. Additionally, β -caryophyllene that had undergone oxidation and caryophyllene hydroperoxides were positive in the local lymph node assay (Skold et al., 2005). In a human maximization test, no reactions indicative of sensitization were observed at 4.0% (2760 $\mu\text{g}/\text{cm}^2$) (RIFM, 1975). In a Confirmation of No Induction in Humans test (CNIH) with 0.65% or (768 $\mu\text{g}/\text{cm}^2$) β -caryophyllene in 1:3 ethanol:DEP (containing 0.1% butylated hydroxy-toluene and 0.1 mm peroxides) no reactions indicative of sensitization were observed in 104 volunteers (RIFM, 2016). No skin sensitization reactions were observed in 2 other CNIHs, conducted with 311 $\mu\text{g}/\text{cm}^2$ and 775 $\mu\text{g}/\text{cm}^2$, respectively (RIFM, 1974a; RIFM, 1974b). In a CNIH conducted at 4% (3101 $\mu\text{g}/\text{cm}^2$), possible sensitization reactions were observed (RIFM, 1971).

Based on the weight of evidence (WoE), β -caryophyllene does not present a safety concern for skin sensitization under the current declared levels of use. The limited studies that indicate a sensitization potential are from the degradation products of β -caryophyllene from autoxidation. This assessment is consistent with data on other terpene compounds, which include similar unsaturated substructures, demonstrating that the pure material is not sensitizing, whereas autoxidation products are known to be contact allergens (i.e., *dl*-limonene CAS # 138-86-3). The chemical structure of β -caryophyllene indicates that it would not have the potential to act as a skin sensitizer directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2; TIMES-SS v2.27.19)*.

*Note: Whereas β -caryophyllene is considered to be non-sensitizing, autoxidation products of this material are shown to be contact allergens (Skold et al., 2005).

Additional References: RIFM, 1999.

Literature Search and Risk Assessment Completed On: 11/02/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, β -caryophyllene would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. The available UV/Vis spectra (OECD test guideline 101) indicate no significant absorbance between 290 and 700 nm. Molar absorption coefficient for wavelengths between 290 and 700 nm is below the benchmark (1000 $\text{L mol}^{-1} \cdot \text{cm}^{-1}$) of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In a guinea pig phototoxicity study, there were no differences in skin reactions of non-irradiated and irradiated test sites exposed to 30% β -caryophyllene; the material was considered a mild irritant. Based on UV/Vis spectra, along with existing data, β -caryophyllene does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1.1. 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 $\text{L mol}^{-1} \cdot \text{cm}^{-1}$

(Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.6. Local respiratory toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on β -caryophyllene. Based on the Creme RIFM Model, the inhalation exposure is 0.012 mg/day. This exposure is 117 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: 11/05/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of β -caryophyllene 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, β -caryophyllene was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified β -caryophyllene as possibly being persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent and bioaccumulative and toxic, or very persistent and very bioaccumulative as defined in the Criteria Document (Api 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.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), β -caryophyllene presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. RIFM, 2007: The ready biodegradability of the test material was conducted using the manometric respirometry test according to the OECD 301 F guideline. Biodegradation of 70% was observed after 28 days.

RIFM, 1995: The ready biodegradability of the test material was conducted using the sealed vessel test according to the OECD 301 B guideline. Biodegradation of 41.2% (95% CI: 33.5–49.0%) was observed after 28 days.

RIFM, 2000: The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301 D guideline. Biodegradation of 10% was observed.

conducted according to the OECD 202 test guidelines under static conditions. The 48-h EC50 value was not determined, but the EC100 value based on nominal test concentration was reported to be > 100 mg/L.

RIFM, 2002a: The *Daphnia magna* immobilization test was conducted according to the OECD 202 test guidelines under static conditions. The 48-h EC50 value was not able to be determined, but the NOEC value was reported to be > 0.17 mg/L.

RIFM, 2017b: The algae growth inhibition test was conducted according to the OECD 201 guideline, under static limit test conditions. As the test item is a volatile substance, the test was performed in a closed system. Due to the low water solubility of the test item, the test solution was prepared by the slow-stirring method at a loading rate of 100 mg/L. The 72-h EC50 values for growth rate yield based on mean measured concentration were reported to be > 0.033 mg/L.

11.2.2.3. Other available data. β -Caryophyllene has been registered under REACH, and no additional data are available at this time.

11.2.2.4. Risk assessment refinement. Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μ g/L).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μ g/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>0.06</u>			1,000,000	0.000060	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	0.027	<u>0.022</u>	0.084	10,000	0.0022	Neutral Organics
Tier 3: Measured Data including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish						
<i>Daphnia</i>		<u>4.6</u>		5,000	0.92	
Algae		> 0.033				

RIFM, 2018: The ready biodegradability of the test material was evaluated using the Headspace test according to the OECD 310 guideline. Biodegradation of 56% was observed after 28 days.

11.2.2.2. Ecotoxicity. RIFM, 2001a: The *Daphnia magna* immobilization test was conducted according to the OECD 202 test guidelines under static conditions. The 48-h EC50 value based on nominal test concentration was reported as 4.6 mg/L (95% CI: 4.3–4.9 mg/L).

RIFM, 2001b: The *Daphnia magna* immobilization test was

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

Exposure	Europe (EU)	North America (NA)
Log Kow Used	6.23	6.23
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	<1	<1

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

The RIFM PNEC is 0.92 µg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 09/11/20.

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:** <https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm>
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **National Library of Medicine's Toxicology Information Services:** <https://toxnet.nlm.nih.gov/>
- **IARC:** <https://monographs.iarc.fr>
- **OECD SIDS:** <https://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVVIS:** https://ofmpub.epa.gov/opthpv/public_search_publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** <https://www.google.com>
- **ChemIDplus:** <https://chem.nlm.nih.gov/chemidplus>

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 9/20/21.

Declaration of competing interest

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

References

- Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. *Food Chem. Toxicol.* 82, S1–S19.
- Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. *Food Chem. Toxicol.* 47 (6), 1287–1295.
- 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.
- DiSotto, A., Evandri, M.G., Mazzanti, G., 2008. Antimutagenic and mutagenic activities of some terpenes in the bacterial reverse mutation assay. *Mutat. Res. Genet. Toxicol. Environ. Mutagen* 653 (1–2), 130–133.
- Echa, 2012. *Guidance on Information Requirements and Chemical Safety Assessment*. November 2012 v2.1. <http://echa.europa.eu/>.
- Hall, A.P., Elcombe, C.R., Foster, J.R., Harada, T., Kaufmann, W., et al., 2012. Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes—conclusions from the 3rd International ESTP expert workshop. *Toxicol. Pathol.* 40 (7), 971–994.
- Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989. An evaluation of food flavoring ingredients in a genetic toxicity screening battery. *Toxicologist* 9 (1), 257.
- Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? *J. Photochem. Photobiol. B Biol.* 96 (1), 57–62.
- IFRA (International Fragrance Association), 2015. *Volume of Use Survey*. February 2015.
- Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. *Food Chem. Toxicol.* 45 (12), 2533–2562.
- Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. *Regul. Toxicol. Pharmacol.* 62 (1), 160–182.
- Lehman-McKeeman, L.D., Caudill, D., 1992. a-2u-globulin is the only member of the lipocalin protein superfamily that binds to hyaline droplet inducing agents. *Toxicol. Appl. Pharmacol.* 116 (2), 170–176.
- Lehman-McKeeman, L.D., Rivera-Torres, M.I., Caudill, D., 1990. Lysosomal degradation of alpha2u-globulin and alpha2u-globulin-xenobiotic conjugates. *Toxicol. Appl. Pharmacol.* 103 (3), 539–548.
- Mollina-Jasso, D., Alvarez-Gonzalez, I., Madrigal-Bujaidar, E., 2009. Clastogenicity of beta-caryophyllene in mouse. *Biol. Pharm. Bull.* 32 (3), 520–522.
- Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2020. Fragrance skin sensitization evaluation and human testing, dermatitis. <https://doi.org/10.1097/DER.0000000000000684>. November 16, 2020. Volume Publish Ahead of Print Issue. Retrieved from.
- RIFM (Research Institute for Fragrance Materials, Inc), 1971. Repeated Insult Patch Test with Beta-Caryophyllene. Unpublished report from International Flavors and Fragrances. RIFM report number 48386. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1974a. Repeated Insult Patch Test with Beta-Caryophyllene. Unpublished report from International Flavors and Fragrances. RIFM report number 48387. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1974b. Repeated Insult Patch Test with Beta-Caryophyllene. Unpublished report from International Flavors and Fragrances. RIFM report number 48388. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1975. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1798. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1984. Mutagenicity Evaluation of Beta-Caryophyllene in the Ames Salmonella/microsome Plate Test. Private Communication to FEMA. Unpublished report from Lorillard Tobacco Company. RIFM report number 36335. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1995. The Biodegradability of Perfume Ingredients in the Sealed Vessel Test. Unpublished report from Quest International. RIFM report number 49701. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1999. Toxicology Studies of Caryophyllene in the guinea Pig. Unpublished report from Takasago International Corporation. RIFM report number 49701. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2000. Beta-Caryophyllene: Biodegradation Test. Unpublished report from Symrise GmbH & Co. KG. RIFM report number 50504. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2001a. Acute Immobilizations Test of Beta-Caryophyllene to Daphnia Magna STRAUS. Unpublished report from Dragoco Gerberding and Co. GmbH. RIFM report number 37774. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2001b. Beta-Caryophyllene: Acute Daphnia Toxicity. Unpublished report from Symrise. RIFM report number 60062. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2002a. Beta-Caryophyllene: Acute Immobilisation Test (48 H) to Daphnia Magna STRAUS. Unpublished report from Symrise GmbH & Co. KG. RIFM report number 50505. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2002b. Beta-Caryophyllene: Water Solubility. Unpublished report from Symrise. RIFM report number 60151. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2007. Ready Biodegradability of Beta-Caryophyllene. Unpublished report from Givaudan. RIFM report number 55348. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2013. Beta-Caryophyllene: 90-Day Dietary Study in Rats. RIFM report number 71651. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2014. Beta-Caryophyllene: A 90-day Dietary Study in Rats. RIFM report number 68494. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2016. Beta-Caryophyllene: Repeated Insult Patch Test (RIPT). RIFM report number 71560. RIFM, Woodcliff Lake, NJ, USA.

- RIFM (Research Institute for Fragrance Materials, Inc), 2017a. Exposure Survey 15. March 2017.
- RIFM (Research Institute for Fragrance Materials, Inc), 2017b. Beta-Caryophyllene (Caryophyllene Nat. rect.): Effect to *Pseudokirchneriella Subcapitata* in a 72-hour Algal Growth Inhibition Test. Unpublished report from Symrise. RIFM report number 72682. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2017c. Beta-Caryophyllene (Caryophyllene Nat. rect.): Determination of the Partition Coefficient (N-octanol/water). Unpublished report from Symrise. RIFM report number 72683. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2017d. beta-Caryophyllene (Caryophyllene Nat. rect.): Determination of Physico-Chemical Properties Melting Point and Boiling Point. Unpublished report from Symrise. RIFM report number 72684. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2017e. Beta-Caryophyllene (Caryophyllene Nat. rect.): Determination of Physico-Chemical Properties Flash Point. Unpublished report from Symrise. RIFM report number 72688. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2018. β -Caryophyllene (Caryophyllene Nat. rect.): Ready Biodegradability in a CO₂ Sealed Vessels (Headspace Test). Unpublished report from Symrise. RIFM report number 74809. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2020. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM report number 76775. 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., 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.
- Sasaki, Y.F., Imanishi, H., Phta, T., Shirasu, Y., 1989. Modifying effects of components of plant essence on the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells. *Mutat. Res. Lett.* 226 (1), 103–110.
- Skold, M., Karlberg, A.-T., Matura, M., Borje, A., 2005. The fragrance chemical beta-caryophyllene-air oxidation and skin sensitization. *Food Chem. Toxicol.* 44 (4), 538–545.
- 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, v2.0. United States Environmental Protection Agency, Washington, DC, USA.