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Short Review

RIFM fragrance ingredient safety assessment β-patchoulene, CAS Registry Number 514-51-2

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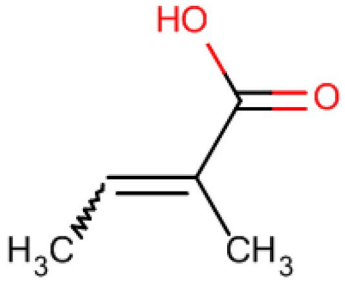
Version: 110217. This version replaces any previous versions.
Name: β-Patchoulene
CAS Registry Number: 514-51-2



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015; 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

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ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment 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 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 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-Patchoulene was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog isolongifolene (CAS # 1135-66-6) show that β-patchoulene is not genotoxic. The skin sensitization endpoint was completed using DST for non-reactive materials (900 μg/cm^2/day); exposure is below the DST. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class II material, and the exposure to β-patchoulene is below the TTC (0.009, 0.009 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra; β-patchoulene is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, β-patchoulene was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are < 1.

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 2014; RIFM, 2015)
Repeated Dose Toxicity: No NOAEL Available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL Available. Exposure is below the TTC.
Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.
(RIFM, 1971; RIFM, 1974; RIFM, 1973)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 61% (OECD 301F) day 65 read-across to longifolene CAS # 175-20-7 (Jenner et al., 2011)
Bioaccumulation: Screening-Level: 3481 L/kg (EPI Suite v4.1)
Ecotoxicity: Screening-Level: 48 h *Daphnia magna* LC50: 0.045 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 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48hr *Daphnia magna* LC50: 0.045 mg/L (EPI Suite v4.1)
RIFM PNEC is: 0.0045 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe < 1

1. Identification

1. **Chemical Name**: β-Patchoulene
2. **CAS Registry Number:** 514-51-2
3. **Synonyms:** 4,7-Methanoazulene, 1,2,3,4,5,6,7,8-octahydro-1,4,9,9-tetramethyl-, [1S-(1alpha,4alpha, 7alpha)]-; (1S-(1a,4a, 7a))-1,2,3,4,5,6,7,8-Octahydro-1,4, 9,9-tetramethyl-4,7-methanoazulene; 1,4,9,9-Tetramethyl-1,2,3,4,5,6,7,8-octahydro-4,7-methanoazulene; β-Patchoulene
4. **Molecular Formula:** $C_{15}H_{24}$
5. **Molecular Weight:** 204.36
6. **RIFM Number:** 6258

2. Physical data

1. **Boiling Point:** 248.65 °C (EPI Suite)
2. **Flash Point:** 211.00 °F. TCC (99.44 °C)*
3. **Log K_{ow}:** 5.87 (EPI Suite)
4. **Melting Point:** 54.95 °C (EPI Suite)
5. **Water Solubility:** 0.1165 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0141 mmHg @ 20 °C (EPI Suite 4.0), 0.007 mm Hg 20C (FMA Database), 0.0244 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Not Available

* http://www.thegoodscentscompany.com/data/rw1045441.html#tophyp, retrieved 12/1/2015.

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.00011% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00000030 mg/kg/day or 0.000018 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.000019 mg/kg/day (RIFM, 2016)

*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 IV. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey 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 II, Intermediate (Expert Judgment)

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

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

2. **Analogs Selected**:
   a. **Genotoxicity:** Isolongifolene (CAS # 1135-66-6)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** Longifolene (CAS # 475-20-7)
3. Read-across Justification: See Appendix below

6. Metabolism

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

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

β-Patchoulene is reported to occur in following foods* and in some natural complex substances (NCS):

7.1. Citrus fruits

*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 that 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 01/24/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, β-patchoulene does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. β-Patchoulene was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013). There are no data assessing the mutagenic activity of β-patchoulene. However, read-across can be made to isolongifolene (CAS # 1135-66-6; see Section V). The mutagenicity of isolongifolene was tested in a GLP compliant Ames assay conducted in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2uvrA were treated with isolongifolene in DMSO (dimethyl sulfoxide) at concentrations up to 5000 µg/plate in the presence and absence of an exogenous mammalian activation system (S9). No increase in the mean frequency of revertant colonies was observed in any of the strains at the concentrations tested with or without metabolic activation (RIFM, 2014). Under the conditions of the study, isolongifolene was considered not mutagenic in bacteria and this can be extended to β-patchoulene.

There are no data assessing the clastogenic activity of β-patchoulene. The clastogenic activity of isolongifolene was assessed in a GLP compliant in vitro micronucleus assay conducted in accordance with OECD TG 487. Human peripheral lymphocytes were treated with isolongifolene in DMSO at concentrations up to 125 µg/ml with and without S9 mix. No statistically significant increase in the frequency of binucleated cells with micronuclei was observed in any treatment condition (RIFM, 2015). Under the conditions of the study, isolongifolene was considered not clastogenic in mammalian cells, and this can be extended to β-patchoulene.

Based on the current existing data and use levels, isolongifolene does not present a concern for genetic toxicity, and this can be extended to β-patchoulene.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/15/2016.

10.1.1.2. Repeated dose toxicity. There are insufficient repeated dose toxicity data on β-patchoulene or any read-across materials. Exposure is below the TTC.

10.1.1.3. Risk assessment. There are no repeated dose toxicity data on β-patchoulene or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure for β-patchoulene (0.019 μg/kg bw/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 6/15/2016.

10.1.2. Developmental and reproductive toxicity

There are insufficient developmental or reproductive toxicity data on β-patchoulene or any read-across materials. Exposure is below the TTC.

10.1.2.1. Risk assessment. There are no developmental or reproductive toxicity data on β-patchoulene or any read-across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure for β-patchoulene (0.019 μg/kg bw/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 3/22/2016.

10.1.3. Skin sensitization

Based on the existing data and application of DST, β-patchoulene does not present a concern for skin sensitization.

10.1.3.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). There are no experimental in vitro or animal studies on β-patchoulene. However, in human repeated insult patch tests no reactions were observed up to 6.25% or 4845 μg/cm2 β-patchoulene in alcohol SDA 39C (RIFM, 1971; RIFM, 1974; RIFM, 1973). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm2. The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentration for β-patchoulene, which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/14/15.

10.1.4. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, β-patchouline would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.4.1. Risk assessment. There are no phototoxicity studies available for β-patchouline in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, β-patchouline does not present a concern for phototoxicity or photoallergenicity.

10.1.4.2. UV spectra analysis. UV/Vis absorption spectra (OECD test guideline 101) for β-patchouline were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, 1000 L $mol^{-1} \cdot cm^{-1}$, of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/20/16.

10.1.5. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, β-patchoulene, exposure level is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.5.1. Risk assessment. There are no inhalation data available on β-patchoulene. Based on the Creme RIFM model, the inhalation exposure is 0.000018 mg/day. This exposure is 26111.1 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the

Table 1
Acceptable concentrations for β-patchoulene based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	95th Percentile Concentration
1	Products applied to the lips	0.069%	0.00%
2	Products applied to the axillae	0.021%	0.000%[b]
3	Products applied to the face using fingertips	0.41%	0.000%[b]
4	Fine fragrance products	0.39%	0.008%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.001%
6	Products with oral and lip exposure	0.23%	0.000%
7	Products applied to the hair with some hand contact	0.79%	0.000%[b]
8	Products with significant ano-genital exposure	0.04%	No Data
9	Products with body and hand exposure, primarily rinse off	0.75%	0.001%
10	Household care products with mostly hand contact	2.70%	0.000%[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.0003%

Note:

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.

[b] Negligible exposure (< 0.01%).

current level of use is deemed safe.

*Cramer Class II defaults to Class III.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/06/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

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

A screening-level hazard assessment using EPI Suite v4.1 identified β-patchoulene as possibly persistent and 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., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.1).

10.2.1.1. Risk assessment. Based on current VoU (IFRA, 2011), β-patchoulene presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2. Biodegradation

No data available.

10.2.3. Ecotoxicity

No data available.

10.2.3.1. Other available data. β-Patchoulene has been pre-registered for REACH with no additional data at this time.

Longifolene CAS# 475-20-7 has been identified as a read-across material, and the following data is available:

Jenner et al., 2011: A ready biodegradability study was conducted according to the OECD 301F method. Biodegradation of 61% was observed after 65 days.

RIFM, 2007: The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F method. Under the conditions of the study biodegradation of 49% was observed.

RIFM, 2009: The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F method. Under the conditions of the study, biodegradation of 61% was observed after 65 days.

10.2.3.2. 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.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	449.3 mg/L			1,000,000	0.4493 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.8	5.8
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.0045 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: 2/10/2016.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml

- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

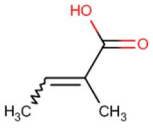
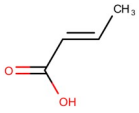
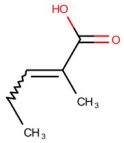
Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2018.03.053.

Appendix

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (EPI Suite, 2012).
- J_{max} 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 generated 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.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was 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	βa-Patchoulene	Isolongifolene	Longifolene
CAS No.	514-51-2	1135-66-6	475-20-7
Structure			
Similarity (Tanimoto score)	1	0.645	0.83
Read-across endpoint		• Genotoxicity	• Environmental
Molecular Formula	$C_{15}H_{24}$	$C_{15}H_{24}$	$C_{15}H_{24}$
Molecular Weight	204.36	204.36	204.36
Melting Point (°C, EPISUITE)	54.95	48.50	46.04
Boiling Point (°C, EPISUITE)	248.65	240.81	239.79
Vapor Pressure (Pa @ 25 °C, EPISUITE)	3.25	5.493	2.493
Log Kow(KOWWIN v1.68 in EPISUITE)	5.87	5.78	5.48
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	0.1165	0.1401	0.2525
J_{max} (mg/cm^2/h, SAM)	0.020426	0.756483838	1.96294577
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	2.33E+004	19717.845	29708.49
Genotoxicity			
DNA binding (OASIS v 1.1 QSAR Toolbox 3.1)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.1)	• No alert found	• No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• Non-carcinogen (low 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	
Metabolism			
OECD QSAR Toolbox (3.1) Rat liver S9 metabolism simulator	See Supplemental Data 1 • 26 metabolites from Rat S9 simulator. • Aldehydes, epoxides, SN2, Schiff base formation, AN2, Michael addition, nucleophilic addition	See Supplemental Data 2 • 8 metabolites from Rat S9 simulator. • No alert found	See Supplemental Data 3

Summary

There are insufficient toxicity data on β-patchoulene (CAS # 514-51-2). Hence *in silico* evaluation was conducted to determine suitable read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogs isolongifolene (CAS # 1135-66-6) and longifolene (CAS # 475-20-7) were identified as read-across materials with data for their

respective toxicological endpoint.

Conclusion/rationale

- Isolongifolene (CAS # 1135-66-6) is used as a structurally similar read-across analog for β-patchoulene (CAS # 514-51-2) for the genotoxicity endpoint.
  - o The target and analog are structurally similar and belong to a class of aliphatic hydrocarbons.
  - o The key difference between the target material and the read-across is that the target has a slightly bigger ring of 7 and 5 carbons while read-across has a 6 and 5 membered ring.
  - o The target and read-across analog have a Tanimoto score of 0.645 which is mainly driven by octahydroazulene fragment. The differences in the structure which are responsible for Tanimoto score < 1 are not relevant from toxicological endpoint perspective.
  - o The physical-chemical properties of the target and the read-across analog are similar.
  - o The structural alerts for the toxicological end points are consistent between the target as well as the read-across material.
  - o The structural alerts show that the read-across material is similarly reactive for the particular endpoints as compared to the target material.
  - o The target and analog are expected to be metabolized similarly as shown by the metabolism simulator. All of the read-across metabolites show no structural alerts for mutagenicity and clastogenicity.
  - o The structural differences between target and the read-across analog appear to be toxicologically insignificant.
- Longifolene was used as a read-across analog for β-patchoulene (CAS# 514-51-2) based on:
  - o The target and analog are structural isomers. They belong to the generic class of aliphatic hydrocarbons, specifically, hydrocarbon/cyclic/tricyclic/bridged/saturated ring.
  - o The key difference is that the target has an unsaturated ring while the analog has a saturated ring.
  - o The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts, and therefore, the toxicity profiles are expected to be similar.
  - o The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

Explanation of cramer class

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, divalent S? No
Q4. Elements not listed in Q3 occurs only as a Na, K, Ca, Mg, N salt, sulfamate, sulfonate, sulfate, hydrochloride? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)?
Q26. Monocycloalkanone or a bicyclo compound? No
Q22. Common component of food? Yes **Intermediate (Class II)**

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