Short Review

RIFM fragrance ingredient safety assessment, myrtenol, CAS Registry Number 515-00-4


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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, 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
- Myrtenol - CAS Registry Number 515-00-4
The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL). A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Myrtenol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that myrtenol is not genotoxic. Data from this material and the read-across analog 2-formyl-6,6-dimethylbicyclo(3.1.1)hept-2-ene (CAS # 564-94-3) show that myrtenol is not a safety concern at the current, declared levels of use for the skin sensitization endpoint. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material, and the exposure to myrtenol is below the TTC (0.03mg/kg/day, 0.03mg/kg/day, and 1.4mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; myrtenol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; myrtenol 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, 2015a; RIFM, 2015b)

**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:** Not a concern for skin sensitization. (RIFM, 2012)

**Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergenic. (UV spectra, RIFM Database)

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

**Environmental Safety Assessment**

**Hazard Assessment:**

- **Persistence:** Screening-level: 2.8 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
- **Bioaccumulation:** Screening-level: 61.88 L/kg (EPI Suite v4.1; US EPA, 2012a)
- **Ecotoxicity:** Screening-level: Fish LC50: 41.35 mg/L (RIFM Framework; Salvito et al., 2002)

**Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards

**Risk Assessment:**

- **Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)**
- **Critical Ecotoxicity Endpoint: Fish LC50: 41.35 mg/L (RIFM Framework; Salvito et al., 2002)**
- **RIFM PNEC is: 0.04135μg/L**

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

1. Chemical Name: Myrtenol
2. CAS Registry Number: 515-00-4
4. Molecular Formulas: C₁₀H₁₆O
5. Molecular Weight: 152.24
6. RIFM Number: 1233

2. Physical data

1. Boiling Point: 224 °C (FMA Database), (calculated) 232.42 °C (EPI Suite)
2. Flash Point: > 200 °F; CC (FMA Database), 94 °C (201 °F) (RIFM Database)
3. Log Kow: 2.8 (EPI Suite)
4. Melting Point: 38.73 °C (EPI Suite)
5. Water Solubility: 426.9 g/L (EPI Suite)
6. Specific Gravity: 0.978–0.983 (RIFM Database)
7. Vapor Pressure: 0.00743 mm Hg @ 20°C (EPI Suite v4.0), 0.006 mm Hg @ 20°C (FMA Database), 0.0137 mm Hg @ 25°C (EPI Suite)
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, almost colorless, liquid with a woody, cooling, minty with a medicinal nuance.


3. Exposure

1. Volume of Use (worldwide band): 0.1–1 metric ton per year (IFRA, 2015)
2. 95th Percentile Concentration in Hydroalcoholics: 0.011% (RIFM, 2014)
3. Inhalation Exposure*: 0.000054 mg/kg/day or 0.0036 mg/day (RIFM, 2014)
4. Total Systemic Exposure**: 0.00037 mg/kg/day (RIFM, 2014)

*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 I, Low

<table>
<thead>
<tr>
<th>Expert Judgment</th>
<th>Toxtree v 2.6</th>
<th>OECD QSAR Toolbox v 3.2</th>
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2. Analogs Selected:
   a. Genotoxicity: None
   b. Repeated Dose Toxicity: None
   c. Developmental and Reproductive Toxicity: None
   d. Skin Sensitization: 2-Formyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (CAS # 564-94-3)
   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 and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

Myrtenol is reported to occur in the following food by the VCF* and some natural complex substances (NCS):

- Buchu Oil.
- Camomile.
- Cheese, Various types.
- Cherimoya (Annona cherimolia Mill.)
- Citrus Fruits.
- Endive (Cichorium endivia L.)
- Eucalyptus Oil (Eucalyptus globulus Labill)
- Ginger (Zingiber species)
- Honey.
- Hop (Humulus lupulus)
- Lamb’s Lettuce (Valerianella locusta)
- Menthias Oils.
- Myrtle (Myrtus communis L.)
- Parsley (Petroselinum species)
- Pepper (Piper nigrum L.)
- Pistachio Oil (Pistacia vera)
- Pistacia Atlantica
- Raspberry, blackberry, and Boysenberry.
- Satureja Species.
- Strawberry (Fragaria species)
- Tea.
- Turpentine Oil (Pistacia terebinthus)
- Vaccinium Species.
- Vanilla.
- Walnut (Juglans species)
- Wormwood Oil (Artemisia absinthium L.)
- Xylopia Species.

8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 11/30/2010; No dossier available as of 11/09/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, myrtenol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Myrtenol tested negative in the BlueScreen assay with and without S9 metabolic activation (RIFM, 2013). The mutagenic activity of myrtenol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with myrtenol in dimethyl sulfoxide (DMSO) 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, 2015b). Under the conditions of the study, myrtenol was not mutagenic in the Ames test.

The clastogenic activity of myrtenol was evaluated in an in vitro micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG487. Human peripheral blood lymphocytes were treated with myrtenol in solvent DMSO at concentrations up to 500 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h. Myrtenol did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2015a). Under the conditions of the study, myrtenol was considered to be non-clastogenic in the in vitro micronucleus test.

Based on the available data, myrtenol does not present a concern for genotoxic potential.


10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on myrtenol or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to myrtenol (0.37 μg/kg/day) is below the TTC (30 μg/kg bw/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 no reproductive toxicity data on myrtenol or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to myrtenol (0.37 μg/kg/day) is below the TTC (30 μg/kg bw/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: 03/10/17.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on myrtenol or any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to myrtenol (0.37 μg/kg/day) is below the TTC (30 μg/kg bw/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 no reproductive toxicity data on myrtenol or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to myrtenol (0.37 μg/kg/day) is below the TTC (30 μg/kg bw/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.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for myrtenol is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on myrtenol. Based on the Creme RIFM Model, the inhalation exposure is 0.0036 mg/day. This exposure is 389 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.


Literature Search and Risk Assessment Completed On: 03/21/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of myrtenol 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 Kow, 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 is applied 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 (USEPA, 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, myrtenol was identified as a fragrance material with no 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 myrtenol as not persistent and not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent and bioaccumulative and toxic, or very persistent and very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

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

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

Other available data: Myrtenol has been pre-registered for REACH with no additional data at this time.

10.2.4. 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.

<table>
<thead>
<tr>
<th>RIFM Framework</th>
<th>LC50 (Fish) (mg/L)</th>
<th>EC50 (Daphnia) (mg/L)</th>
<th>EC50 (Algae) (mg/L)</th>
<th>AF</th>
<th>PNEC (μg/L)</th>
<th>Chemical Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening-level (Tier 1)</td>
<td>41.35</td>
<td></td>
<td></td>
<td></td>
<td>0.04135</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Europe (EU)</th>
<th>North America (NA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Kow used</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Biodegradation Factor Used</td>
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<td>1</td>
</tr>
<tr>
<td>Dilution Factor</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Regional Volume of Use Tonnage Band</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

**Risk Characterization: PEC/PNEC < 1 < 1**

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

The RIFM PNEC is 0.04135 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level 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: 01/17/14.

11. Literature Search*

- RIFM Database: Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110602.

Appendix

Read-across justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- Jmax values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

<table>
<thead>
<tr>
<th>Principal Name</th>
<th>Target material</th>
<th>Read-across material</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS No.</td>
<td>Myrtenol 515-00-4</td>
<td>2-Formyl-6,6-dimethylbicyclo(3.1.1)hept-2-ene 564-94-3</td>
</tr>
<tr>
<td>Structure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Similarity (Tanimoto score) | 0.86 |
| Read-across endpoint | Skin Sensitization |
| Molecular Formula | C_{12}H_{20}O | C_{14}H_{24}O |
| Molecular Weight | 152.24 | 208.35 |
| Melting Point (°C, EPI Suite) | 38.73 | 60.19 |
| Boiling Point (°C, EPI Suite) | 224 | 199 |
| Vapor Pressure (Pa @ 25 °C, EPI Suite) | 0.0137 | 0.128 |
| Log Kow (KOWWIN v1.68 in EPI Suite) | 3.22 | 4.3 |
| Water Solubility (mg/L @ 25 °C, WSKOW v1.42 in EPI Suite) | 426.9 | 215.9 |
| Jmax (μg/cm²/h, SAM) | 685.417 | 152.722 |
| Henry’s Law (Pa m³/mol, Bond Method, EPI Suite) | 7.05E-001 | 7.14E+000 |
| Skin Sensitization | No alert found |
| Protein binding by OASIS v1.1 | AN2 Michael addition Schiff base formation |
Protein binding by OECD
- No alert found
- Michael addition
- Schiff base formation

Protein binding potency
- Not possible to classify (GSH)
- Moderately reactive (GSH), substituted 2-alken-1-al (Michael addition)
- Schiff base formation

Skin Sensitization alerts by OASIS v1.1
- Sensitizer (good reliability)
- Sensitizer (good reliability)

Metabolism
- Rat liver S9 metabolism simulator and structural alerts for metabolites

OECD QSAR Toolbox (v3.4)
- See Supplemental Data 1
- See Supplemental Data 2


Summary
There are insufficient toxicity data on the target material myrtenol (CAS # 515-00-4). Hence, in silico evaluation determined a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties, and expert judgment, 2-formyl-6,6-dimethylbicyclo(3.1.1)hept-2-ene (CAS # 564-94-3) was identified as a read-across material with sufficient data for toxicological evaluation.

Metabolism
Metabolism of the target material myrtenol (CAS # 515-00-4) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). The target material is predicted to be metabolized to 2-formyl-6,6-dimethylbicyclo(3.1.1)hept-2-ene (CAS # 564-94-3) in the first step with 0.95 probability. Hence, 2-formyl-6,6-dimethylbicyclo(3.1.1)hept-2-ene (CAS # 564-94-3) can be used as a read-across analog for the target material. Read-across material 2-formyl-6,6-dimethylbicyclo(3.1.1)hept-2-ene (CAS # 564-94-3) was in domain for the in vitro rat S9 simulator (OASIS TIMES v2.27.19).

12. Conclusions
- 2-Formyl-6,6-dimethylbicyclo(3.1.1)hept-2-ene (CAS # 564-94-3) was used as a read-across analog for the target material myrtenol (CAS # 515-00-4) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and share the same unsaturated cyclic alkene extended fragment.
  - The read-across analog and the target substance are metabolites of each other. The Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4) predicts the metabolic redox conversion between the primary alcohol and an aldehyde.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table.
  - The physical-chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - The read-across analog has AN2, Michael addition, and Schiff base formation alerts for the skin sensitization endpoint. This is due to the fact that the read-across analog is an activated (α,β-unsaturated) aldehyde which can very well be a Michael acceptor, undergo nucleophilic attack, and form a Schiff base with a protein or a nucleic acid nitrogen atom. The target material is expected to be more reactive upon metabolic transformation from alcohol to aldehyde. The read-across analog is a direct step 1 metabolite of the target material. The alerts confirm that the read-across analog is expected to be more reactive compared to the target material. Based on the structural similarity and the predicted metabolic transformation between the target material and the read-across analog as well as existing data for the read-across material described in the skin sensitization section, which shows that the read-across analog does not present a concern for skin sensitization, the alert will be superseded by the data.
  - The target substance and the read-across analog are predicted to be sensitizers by the CAESAR model for skin sensitization. Existing data for the read-across material described in the skin sensitization section shows that the read-across analog does not present a concern for skin sensitization. Therefore, the alert will be superseded by the data.

References


A.M. Api, et al.  

Food and Chemical Toxicology 130 (2019) 110602