



## Short review

## RIFM fragrance ingredient safety assessment, 2-tert-butylcyclohexanol, CAS Registry Number 13491-79-7



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**Version: 042617.** This version replaces any previous versions.

**Name:** 2-tert-Butylcyclohexanol

**CAS Registry Number:** 13491-79-7

**Additional CAS Numbers\*:**

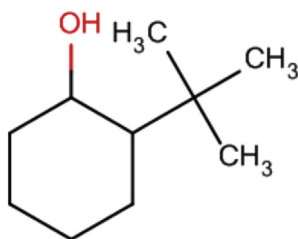
7214-18-8 *cis*-2-tert-

Butylcyclohexan-1-ol

5448-22-6 *trans*-2-tert-

Butylcyclohexan-1-ol

\*These materials were included because they are a mixture of isomers

**Abbreviation list:**

**2-Box Model** – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

**AF** – Assessment Factor

**BCF** – Bioconcentration Factor

**Creme RIFM model** – The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017) compared to a deterministic aggregate approach.

**DEREK** – Derek nexus is an *in silico* tool used to identify structural alerts

**DST** – Dermal Sensitization Threshold

**ECHA** – European Chemicals Agency

**EU** – Europe/European Union

**GLP** – Good Laboratory Practice

**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

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**NOEC** - No Observed Effect Concentration  
**OECD** - Organisation for Economic Co-operation and Development  
**OECD TG** - Organisation for Economic Co-operation and Development Testing Guidelines  
**PBT** - Persistent, Bioaccumulative, and Toxic  
**PEC/PNEC** - Predicted Environmental Concentration/Predicted No Effect Concentration  
**QRA** - Quantitative Risk Assessment  
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals  
**RIFM** - Research Institute for Fragrance Materials  
**RQ** - Risk Quotient  
**TTC** - Threshold of Toxicological Concern  
**UV/Vis Spectra** - Ultra Violet/Visible spectra  
**VCF** - Volatile Compounds in Food  
**VoU** - Volume of Use  
**vPvB** - (very) Persistent, (very) Bioaccumulative  
**WOE** - Weight of Evidence

**The Expert Panel for Fragrance Safety\* concludes that this material is safe under the limits described in this safety assessment.**

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

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

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

**Summary: The use of this material under current conditions is supported by existing information.**

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from read across analogs, 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol (CAS # 67634-11-1) and 4-tert-butylcyclohexanol (CAS # 98-52-2), show that this material does not have the potential for skin sensitization. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class 1 material (0.023 mg/kg/day). The repeated dose, developmental and reproductive toxicity endpoints were completed using 2-tert-butylcyclohexyl acetate (CAS # 88-41-5) and cis-2-tert-butylcyclohexyl acetate (CAS # 20298-69-5) as read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated and this material was not found to be a PBT; its risk quotients, based on current volume of use in Europe and North America, were acceptable (PEC/PNEC < 1).

#### Human Health Safety Assessment

**Genotoxicity:** Not genotoxic. (RIFM, 1998; RIFM, 2014a)

**Repeated Dose Toxicity:** (JECDB, 2013)

NOAEL = 50 mg/kg/day

**Developmental and Reproductive** (JECDB, 2013)

**Toxicity:** NOAEL = 150 mg/kg/day

**Skin Sensitization:** Not sensitizing. (RIFM, 1973a, b, c; RIFM, 1964a; RIFM, 1964b)

**Phototoxicity/Photoallergenicity:** (UV Spectra, RIFM DB)  
 Not phototoxic/photoallergenic.

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

#### Environmental Safety Assessment

##### Hazard Assessment:

**Persistence:** Screening Level: 62% (RIFM, 2010a, b)  
 (OECD 301F)

**Bioaccumulation:** Screening Level: 3.48 l/kg (EpiSuite ver 4.1)

**Ecotoxicity:** Screening Level: (EpiSuite ver 4.1)  
 48 h *Daphnia magna* LC50:  
 4.434 mg/l

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

#### Risk Assessment:

**Screening-Level:** PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)

**Critical Ecotoxicity Endpoint:** 48 h (Epi Suite ver 4.1)

*Daphnia magna* LC50: 4.434 mg/l

**RIFM PNEC is:** 0.4434 µg/L

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

## 1. Identification

Chemical Name: 2-tert-Butylcyclohexanol	Chemical Name: cis-2-tert-Butylcyclohexan-1-ol	Chemical Name: trans-2-tert-Butylcyclohexan-1-ol
<b>CAS Registry Number:</b> 13491-79-7	<b>CAS Registry Number:</b> 7214-18-8	<b>CAS Registry Number:</b> 5448-22-6
<b>Synonyms:</b> 2-tert-Butylcyclohexanol; Cyclohexanol, 2-(1,1-dimethylethyl)-; 2-(1,1-Dimethylethyl) cyclohexanol; 7ルキル(C = 1-5) シロキル-ル; Verdol; Terranol	<b>Synonyms:</b> cis-2-tert-Butylcyclohexan-1-ol; 2-tert-Butylcyclohexanol; Cyclohexanol, 2-(1,1-dimethylethyl)-, cis-	<b>Synonyms:</b> trans-2-tert-Butylcyclohexan-1-ol; 2-tert-Butylcyclohexanol; Cyclohexanol, 2-(1,1-dimethylethyl)-, trans-; Verdol
<b>Molecular Formula:</b> C <sub>10</sub> H <sub>20</sub> O	<b>Molecular Formula:</b> C <sub>10</sub> H <sub>20</sub> O	<b>Molecular Formula:</b> C <sub>10</sub> H <sub>20</sub> O
<b>Molecular Weight:</b> 156.69	<b>Molecular Weight:</b> 156.69	<b>Molecular Weight:</b> 156.69
<b>RIFM Number:</b> 5407	<b>RIFM Number:</b> 5359	<b>RIFM Number:</b> 5331

## 2. Physical data\*

- Boiling Point:** 216.91 °C [EPI Suite]
- Flash Point:** 78 °C [GHS]
- Log K<sub>ow</sub>:** 3.42 [EPI Suite]
- Melting Point:** 4.34 °C [EPI Suite]
- Water Solubility:** 278 mg/L [EPI Suite]
- Specific Gravity:** Not Available
- Vapor Pressure:** 0.0086 mmHg @ 20 °C (EPI Suite 4.0), 0.0158 mm Hg @ 25 °C [EPI Suite]
- UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol<sup>-1</sup> cm<sup>-1</sup>)
- Appearance/Organoleptic:** A crystalline mass which has a powerful, camphoraceous-piney, mostly minty and somewhat tarry odor of great tenacity.

\*Physical data for all materials included in this assessment are identical.

## 3. Exposure\*\*\*

- Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2011)
- 95th Percentile Concentration in Hydroalcohols:** 0.073% (RIFM, 2014b)
- Inhalation Exposure\*:** 0.00039 mg/kg/day or 0.028 mg/day (RIFM, 2014b)
- Total Systemic Exposure \*\*:** 0.0021 mg/kg/day (RIFM, 2014b)

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

\*\*95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015 and Safford et al., 2017).

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

#### 4. Derivation of systemic absorption

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

#### 5. Computational toxicology evaluation

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

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

#### 2. Analogues Selected:

- a. **Genotoxicity:** None
  - b. **Repeated Dose Toxicity:** 2-*tert*-Butylcyclohexyl acetate (CAS # 88-41-5); *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5)
  - c. **Developmental and Reproductive Toxicity:** 2-*tert*-Butylcyclohexyl acetate (CAS # 88-41-5); *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5)
  - d. **Skin Sensitization:** 2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol (CAS # 67634-11-1) and 4-*tert*-Butylcyclohexanol (CAS # 98-52-2)
  - 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)

2-*tert*-Butylcyclohexanol, *cis*-2-*tert*-butylcyclohexan-1-ol, and *trans*-2-*tert*-butylcyclohexan-1-ol are not reported to occur in food by the VCF\*.

\*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually

updated database, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

#### 8. IFRA standard

None.

#### 9. REACH dossier

Pre-registered for 2013; no dossier available as of 04/26/2017. *cis*-2-*tert*-Butylcyclohexan-1-ol has a dossier available, accessed 4/26/2017. *trans*-2-*tert*-Butylcyclohexan-1-ol is pre-registered for 2010, no dossier available as of 4/26/2017.

#### 10. Summary

##### 10.1. Human health endpoint summaries

##### 10.1.1. Genotoxicity

Based on the current existing data, 2-*tert*-butylcyclohexanol does not present a concern for genetic toxicity.

**10.1.1.1. Risk assessment.** 2-*tert*-butylcyclohexanol was tested using the BlueScreen assay and found to be non-genotoxic with and without S9 metabolic activation (RIFM, 2015). The mutagenicity of 2-*tert*-butylcyclohexanol was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were treated with 2-*tert*-butylcyclohexanol in dimethyl sulfoxide (DMSO) at concentrations up to 2250 µg/plate in the presence and absence of metabolic activation (S9). No significant increase in the number of revertant colonies was observed in any strain at any dose, with or without S9 mix (RIFM, 1998). Under the conditions of the study, 2-*tert*-butylcyclohexanol was considered not to be mutagenic in bacteria.

The clastogenicity of 2-*tert*-butylcyclohexanol was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral lymphocytes were treated with 2-*tert*-butylcyclohexanol in DMSO at concentrations up to 300 µg/mL in the presence and absence of metabolic activation (S9). No statistically significant increases in the frequency of cells with micronuclei were observed (RIFM, 2014a). Under the conditions of the study, 2-*tert*-butylcyclohexanol was considered not clastogenic.

Based on the available data, 2-*tert*-butylcyclohexanol does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 9/20/2015.

##### 10.1.2. Repeated dose toxicity

The margin of exposure for 2-*tert*-butylcyclohexanol is adequate for the repeated dose endpoint.

**10.1.2.1. Risk assessment.** There are no repeated dose toxicity data on 2-*tert*-butylcyclohexanol. 2-*tert*-Butylcyclohexanol is the likely metabolite of 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5; see Section 5) and *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5; see Section 5). 2-*tert*-Butylcyclohexyl acetate has a gavage combined repeated dose toxicity study and reproduction/developmental toxicity screening test conducted in rats which determined the NOAEL to be 50 mg/kg/day, based on centrilobular hepatocyte hypertrophy (JECDB, 2013). *cis*-2-*tert*-Butylcyclohexyl acetate has an OECD 422 dietary combined repeated dose toxicity

study and reproduction/developmental toxicity screening test in rats which determined the NOAEL to be 437 mg/kg/day, the highest dosage tested (RIFM, 2012). The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 50/0.0021 or 23810.

**Additional References:** Cheo et al., 1967; Treon et al., 1943a, 1943b; ECHA REACH Dossier: trans-4-tert-Butylcyclohexanol; RIFM, 2010a, b; RIFM, 1979; RIFM, 1973c; Hotchkiss, 1998; RIFM, 2008a; RIFM, 2008b; JECFA, 1999a; JECFA, 1999b; JECFA, 2000; Hayes et al., 2007; Imaizumi et al., 1985; Fox, 1930; Kaffenberger and Doyle, 1990; Quick, 1928; Gelal et al., 2005; Longenecker et al., 1939; Spichiger et al., 2004; Williams, 1938; Martin et al., 2004; Meyer, 1965; Songkro et al., 2003; Chen et al., 2004; Gao and Singh, 1998; RIFM, 2008c; RIFM, 2008d; MacDougall et al., 2003; Green and Tephly, 1996; Robin et al., 1998; RIFM, 2008e; Kowalski et al., 1962; Stoner et al., 1973; Rakiety et al., 1954; Thorup et al., 1983; Pereira et al., 2007; Somerville et al., 1984; White et al., 1987; Quick, 1924; Deichmann and Thomas, 1943; Boutin et al., 1983, 1981, 1985; Schafer and Schafer, 1982; Macht, 1939; Williams, 1940; RIFM, 2008f; Levvy et al., 1948; Pinching and Doving, 1974; Hasegawa and Toda, 1978; Madyastha and Srivatsan, 1988; Bell et al., 1981; Wright, 1945; Gelal et al., 1999; Yamaguchi et al., 1994; Godwin and Michniak, 1999; RIFM, 2008g; Belsito et al., 2008; RIFM, 2008h.

**Literature Search and Risk Assessment Completed on:** 04/23/15.

### 10.1.3. Developmental and reproductive toxicity

The margin of exposure for 2-tert-butylcyclohexanol is adequate for the developmental and reproductive endpoint.

**10.1.3.1. Risk assessment.** There are no developmental toxicity data on 2-tert-butylcyclohexanol. 2-tert-Butylcyclohexanol is the likely metabolite of 2-tert-butylcyclohexyl acetate (CAS # 88-41-5; see Section 5) and cis-2-tert-butylcyclohexyl acetate (CAS # 20298-69-5; see Section 5). 2-tert-Butylcyclohexyl acetate has a gavage combined repeated dose toxicity study and reproduction/developmental toxicity screening test conducted in rats which determined the NOAEL in pups to be 150 mg/kg/day, based on a trend towards reduced pup bodyweight gain (JECDB, 2013). cis-2-tert-Butylcyclohexyl acetate has an OECD 422 dietary combined repeated dose toxicity study and reproduction/developmental toxicity screening test in rats which determined the NOAEL to be 437 mg/kg/day for developmental toxicity, the highest dosage tested (RIFM, 2012). Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 150/0.0021 or 71429.

There are no reproductive toxicity data on 2-tert-butylcyclohexanol. 2-tert-Butylcyclohexanol is the likely metabolite of 2-tert-butylcyclohexyl acetate (CAS # 88-41-5) and cis-2-tert-butylcyclohexyl acetate (CAS # 20298-69-5). 2-tert-Butylcyclohexyl acetate has a gavage combined repeated dose toxicity study and reproduction/developmental toxicity screening test conducted in rats which determined the NOAEL for fertility to be 500 mg/kg/day, the highest dosage tested (JECDB, 2013). cis-2-tert-Butylcyclohexyl acetate has an OECD 422 dietary combined repeated dose toxicity study and reproduction/developmental toxicity screening test in rats which determined the NOAEL to be 437 mg/kg/day for reproductive toxicity, the highest dosage tested (RIFM, 2012). The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 437/0.0021 or 208295.

**Additional References:** Cheo et al., 1967; Treon et al., 1943a, 1943b; ECHA REACH Dossier: trans-4-tert-Butylcyclohexanol; RIFM, 2010a, b; RIFM, 1979; RIFM, 1973c; Hotchkiss, 1998; RIFM,

2008a; RIFM, 2008b; JECFA, 1999a; JECFA, 1999b; JECFA, 2000; Hayes et al., 2007; Imaizumi et al., 1985; Fox, 1930; Kaffenberger and Doyle, 1990; Quick, 1928; Gelal et al., 2005; Longenecker et al., 1939; Spichiger et al., 2004; Williams, 1938; Martin et al., 2004; Meyer, 1965; Songkro et al., 2003; Chen et al., 2004; Gao and Singh, 1998; RIFM, 2008c; RIFM, 2008d; MacDougall et al., 2003; Green and Tephly, 1996; Robin et al., 1998; RIFM, 2008e; Kowalski et al., 1962; Stoner et al., 1973; Rakiety et al., 1954; Thorup et al., 1983; Pereira et al., 2007; Somerville et al., 1984; White et al., 1987; Quick, 1924; Deichmann and Thomas, 1943; Boutin et al., 1983, 1981, 1985; Schafer and Schafer, 1982; Macht, 1939; Williams, 1940; RIFM, 2008f; Levvy et al., 1948; Pinching and Doving, 1974; Hasegawa and Toda, 1978; Madyastha and Srivatsan, 1988; Bell et al., 1981; Wright, 1945; Gelal et al., 1999; Yamaguchi et al., 1994; Godwin and Michniak, 1999; RIFM, 2008g; Belsito et al., 2008; RIFM, 2008h.

**Literature Search and Risk Assessment Completed on:** 04/23/15.

### 10.1.4. Skin sensitization

Based on the existing data on the additional material trans-2-tert-butylcyclohexan-1-ol (CAS # 5448-22-6) and the read across materials 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol (CAS # 67634-11-1) and 4-tert-butylcyclohexanol (CAS # 98-52-2), 2-tert-butylcyclohexanol does not present a concern for skin sensitization.

**10.1.4.1. Risk assessment.** No skin sensitization data exist for 2-tert-butylcyclohexanol. The chemical structures of the target, additional material and read across materials (see Section 5) indicate that they would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In guinea pig sensitization tests no reactions indicative of sensitization were observed with the read across material 4-tert-butylcyclohexanol (Klecak, 1985; ECHA REACH Dossier). Human repeat insult patch tests (HRIPT) with 194 µg/cm<sup>2</sup> of additional material trans-2-tert-butylcyclohexan-1-ol and read across materials, 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol, and 4-tert-butylcyclohexanol, did not produce reactions indicative of sensitization (RIFM, 1973b; RIFM, 1964b; RIFM, 1964a). In the human maximization test, no reactions indicative of sensitization were observed with 4-tert-butylcyclohexanol (RIFM, 1973a).

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 05/01/15.

### 10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, on 2-tert-butylcyclohexanol would not be expected to present a concern for phototoxicity or photoallergenicity.

**10.1.5.1. Risk assessment.** There are no phototoxicity studies available for on 2-tert-butylcyclohexanol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol<sup>-1</sup> cm<sup>-1</sup> (Henry et al., 2009). Based on lack of absorbance, on 2-tert-butylcyclohexanol does not present a concern for phototoxicity or photoallergenicity.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 05/23/16.

### 10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The inhalation exposure is below the TTC at the current level of use.



**10.1.6.1. Risk assessment.** Based on the Creme RIFM model, the inhalation exposure is 0.028 mg/day. This exposure is 50 times lower than the TTC for a Cramer Class I material (1.4 mg/day); therefore, the exposure at the current level of use is deemed safe.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 11/02/2015.

## 10.2. Environmental endpoint summary

### 10.2.1. Screening-level assessment

A screening level risk assessment of 2-*tert*-butylcyclohexanol 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

**10.2.1.1. Risk assessment.** Based on current Volume of Use (2011), 2-*tert*-butylcyclohexanol presents a risk to the aquatic compartment in the screening level assessment.

**10.2.1.2. Biodegradation.** RIFM, 2010a, 2010b: The ready biodegradability of the test material was evaluated according to the Manometric Respirometry Test according to the OECD 301F method. Under the conditions of the study, biodegradation of 62% was observed after 28 days.

**10.2.1.3. Ecotoxicity.** No data available.

**10.2.1.4. Other available data.** 2-*tert*-Butylcyclohexanol has been pre-registered for REACH with no additional data at this time.

### 10.3. 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)	<u>12.29 mg/L</u>			1,000,000	0.01229 µg/L	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	6.851 mg/L	<u>4.434 mg/L</u>	5.764 mg/L	10,000	0.4434 µg/L	Neutral Organics

(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, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 2-*tert*-butylcyclohexanol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (*i.e.*, its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify 2-*tert*-butylcyclohexanol as possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (*e.g.*, OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (*e.g.*, USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section.

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

Exposure	Europe (EU)	North America (NA)
Log $K_{ow}$ used	2.1	2.1
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1-10*	<1*
<b>Risk Characterization: PEC/PNEC</b>	<b>&lt;1</b>	<b>&lt;1</b>

\*Combined Regional Volumes for all CAS#

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

The RIFM PNEC is 0.4434 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:** 4/21/15.

## 11. Literature search\*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <http://echa.europa.eu/>

- **NTP:** [http://tools.niehs.nih.gov/ntp\\_tox/index.cfm](http://tools.niehs.nih.gov/ntp_tox/index.cfm)
- **OECD Toolbox**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PUBMED:** <http://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <http://toxnet.nlm.nih.gov/>
- **IARC:** (<http://monographs.iarc.fr>)
- **OECD SIDS:** <http://www.chem.unep.ch/irptc/sids/oecd/sids/sidspub.html>
- **EPA Actor:** <http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7>
- **US EPA HPVIS:** <http://www.epa.gov/hpv/hpvis/index.html>
- **US EPA Robust Summary:** <http://cfpub.epa.gov/hpv-s/>
- **Japanese NITE:** <http://www.safe.nite.go.jp/english/db.html>
- **Japan Existing Chemical Data Base:** [http://dra4.nihs.go.jp/mhlw\\_data/jsp/SearchPageENG.jsp](http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp)
- **Google:** <https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4>

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

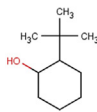
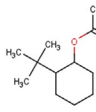
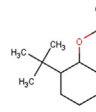
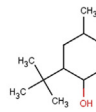
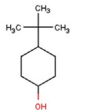
## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2017.05.062>.

## Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2017.05.062>.

## Appendix

	Target Material	Read across Material			
<b>Principal Name</b>	2-tert-Butylcyclohexanol	2-tert-Butylcyclohexyl acetate	cis-2-tert-Butylcyclohexyl acetate	2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol	4-tert-Butylcyclohexanol
<b>CAS No.</b>	13491-79-7	88-41-5	20298-69-5	67634-11-1	98-52-2
<b>Structure</b>					
<b>3D Structure</b>	<a href="http://www.thegoodscentscompany.com/opl/13491-79-7.html">http://www.thegoodscentscompany.com/opl/13491-79-7.html</a>	<a href="http://www.thegoodscentscompany.com/opl/88-41-5.html">http://www.thegoodscentscompany.com/opl/88-41-5.html</a>	<a href="http://www.thegoodscentscompany.com/opl/20298-69-5.html">http://www.thegoodscentscompany.com/opl/20298-69-5.html</a>	<a href="http://www.thegoodscentscompany.com/opl/67634-11-1.html">http://www.thegoodscentscompany.com/opl/67634-11-1.html</a>	<a href="http://www.thegoodscentscompany.com/opl/98-52-2.html">http://www.thegoodscentscompany.com/opl/98-52-2.html</a>
<b>Read-across endpoint</b>		•Repeated Dose •Devel/Repro	•Repeated Dose •Devel/Repro	•Skin sensitization	•Skin sensitization
<b>Molecular Formula</b>	C10H20O	C12H22O2	C12H22O2	C11H22O	C10H20O
<b>Molecular Weight</b>	156.27	198.31	198.31	170.3	156.27
<b>Melting Point (°C, EPISUITE)</b>	4.34	10.93	10.93	11.75	4.34
<b>Boiling Point (°C, EPISUITE)</b>	216.91	232.55	232.55	230.26	216.91
<b>Vapor Pressure</b>	2.106	7.106	7.106	1.52	1.44

(Pa @ 25°C, EPISUITE)					
Log K <sub>ow</sub> (KOWWIN v1.68 in EPISUITE)	3.42	4.42	4.42	3.83	3.42
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	278	7.462	7.462	105.3	528.9
J <sub>max</sub> (µg/cm <sup>2</sup> /h, SAM)	49.58658348	17.07952394	17.07952394	30.31066927	57.2551079
Henry's Law (Pa·m <sup>3</sup> /mol, Bond Method, EPISUITE)	1.541153	100.321883	100.321883	2.045752	1.541153
Similarity (Tanimoto score) <sup>1</sup>		NA <sup>2</sup>	NA <sup>2</sup>	81%	68%
<b>Repeated Dose Toxicity</b>					
<b>Repeated dose (HESS)</b>	Not categorized	Not categorized	Not categorized		
<b>Developmental and Reproductive Toxicity</b>					
<b>ER binding (OECD)</b>	Weak binder, OH group	Non binder, without OH or NH <sub>2</sub> group	Non binder, without OH or NH <sub>2</sub> group		
<b>Developmental</b>	Toxicant (good reliability)	Toxicant (moderate)	Toxicant (moderate)		

(continued).

<b>toxicity model</b> (CAESAR v2.1.6)		reliability)	reliability)		
<b>Skin Sensitization</b>					
<b>Protein binding</b> (OASIS v1.1)	•No alert found			•No alert found	•No alert found
<b>Protein binding</b> (OECD)	•No alert found			•No alert found	•No alert found
<b>Protein binding</b> <b>potency (OECD)</b>	•Not possible to classify according to these rules (GSH)			•Not possible to classify according to these rules (GSH)	•Not possible to classify according to these rules (GSH)
<b>Protein binding</b> <b>alerts for skin sensitization (OASIS v1.1)</b>	•No alert found			•No alert found	•No alert found
<b>Skin sensitization model (CAESAR v2.1.6)</b>	Sensitizer (good reliability)			Sensitizer (good reliability)	Sensitizer (good reliability)
<b>Metabolism</b>					
<b>Rat liver S9 metabolism simulator (OECD)</b>	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

<sup>1</sup> Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn 2010).

<sup>2</sup> The metabolite of the analog is the target.

(continued).

## Summary

There are insufficient toxicity data on 2-*tert*-butylcyclohexanol (RIFM# 5407, CAS# 13491-79-7). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

## Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The  $J_{max}$  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 estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity and skin sensitization were estimated using CAESAR (v2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Tanimoto values were calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010)

## Conclusion/Rationale

- 2-*tert*-Butylcyclohexyl acetate and *cis*-2-*tert*-butylcyclohexyl acetate (analog) were used as a read-across analog for 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol (target) based on:
  - o The analogs are expected to be metabolized into the target and thus were determined to be suitable analogs. 2-*tert*-Butylcyclohexyl acetate is an ester formed by acetic acid and 2-*tert*-Butylcyclohexyl alcohol. Therefore, the toxicity profile is expected to be that of the metabolites.



- o The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER binding. ER binding is molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
- o As per the OECD Toolbox, the analogs are predicted to be metabolized into 2-*tert*-butylcyclohexyl alcohol.
- *Trans*-2-*tert*-Butylcyclohexan-1-ol is a stereoisomer of the target. Stereoisomers have the same atomic connectivity but differ in spatial arrangement of atoms or functional groups and usually behave in a similar chemical and toxicological manner.
- 2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol (analog) was used as a read-across analog for 2-*tert*-butylcyclohexanol (target) based on:
  - o The target and analog belong to the generic class of alcohols, specifically, alcohol/cyclic/monocyclic/secondary alcohols/saturated.
  - o The target and analog has the same function groups of alcohol and *t*-butyl substitute.
  - o The key difference is that the analog has an additional methyl group. 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 show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - o The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER binding. ER binding is molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - o The target and analog show similar alerts for protein binding.
  - o The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.
- 4-*tert*-Butylcyclohexanol (analog) was used as a read-across analog for 2-*tert*-butylcyclohexanol (target) based on:
  - o The target and analog belong to the generic class of alcohols, specifically, alcohol/cyclic/monocyclic/secondary alcohols/saturated.
  - o The target and analog has the same function groups of alcohol and *t*-butyl substitute.
  - o The key difference is in the position of the substitutes. The analog has the *t*-butyl group in the para position, while the target has the *t*-butyl group in the meta position. 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 show similar alerts for protein binding.
  - o The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

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