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RIFM fragrance ingredient safety assessment, *p-tert*-butylcyclohexanone, CAS Registry Number 98-53-3

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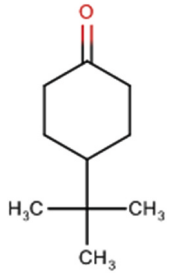

Name: *p-tert*-Butylcyclohexanone
CAS Registry Number: 98-53-3

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable

(*continued on next column*)

(*continued*)

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 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.

p-tert-Butylcyclohexanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data and read-across to 2-*tert*-butylcyclohexanone (CAS # 1728-46-7) show that *p-tert*-butylcyclohexanone is not expected to be genotoxic. Data on read-across material 2-sec-butylcyclohexanone (CAS # 14765-30-1) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from read-across analog 4-*t*-amylcyclohexanone (CAS # 16587-71-6) provided a No Expected Sensitization Induction Level (NESIL) of 350 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; *p-tert*-butylcyclohexanone is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to *p-tert*-butylcyclohexanone is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; *p-tert*-butylcyclohexanone was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: 4-tert-Butylcyclohexanone; ECHA, 2011; RIFM, 2017)
Repeated Dose Toxicity: NOAEL = 16 mg/kg/day.	RIFM (2018)
Reproductive Toxicity: Developmental toxicity: 226 mg/kg/day. Fertility: 226 mg/kg/day.	RIFM (2018)
Skin Sensitization: NESIL = 350 μg/cm^2.	RIFM (2012b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 32% (OECD 301D)	(ECHA REACH Dossier: 4-tert-Butylcyclohexanone; ECHA, 2011)
Bioaccumulation:	
Screening-level: 38.3 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 33.61 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: 33.61 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.03361 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** *p-tert*-Butylcyclohexanone
2. **CAS Registry Number:** 98-53-3
3. **Synonyms:** 4-*tert*-Butylcyclohexanone; Cyclohexanone, 4-(1,1-dimethylethyl)-; ｱﾙｷﾙ(C = 1–5)ｼｸﾛﾍｷｻﾉﾝ; *p-tert*-Butylcyclohexanone
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25
6. **RIFM Number:** 530

7. **Stereochemistry:** Isomer not specified. One chiral center and 2 enantiomers possible.

2. Physical data

1. **Boiling Point:** 113 °C at 20 mm Hg (Fragrance Materials Association [FMA]), 210.92 °C (EPI Suite)
2. **Flash Point:** 95 °C (Globally Harmonized System), 190 °F; CC (FMA)
3. **Log K_{OW}:** 2.91 (EPI Suite)
4. **Melting Point**: 40–50 °C (FMA), 8.41 °C (EPI Suite)
5. **Water Solubility:** 239.8 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.105 mm Hg at 20 °C (EPI Suite v4.0), 0.06 mm Hg at 20 °C (FMA), 0.173 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless or white crystals with a powerful, dry-camphoraceous, slightly minty odor with woody cedary-patchouli-like undertones

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0060% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.000044 mg/kg/day or 0.0033 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.00034 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 V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	II	II

2. Analogs Selected:
   a. **Genotoxicity:** 2-*tert*-Butylcyclohexanone (CAS # 1728-46-7)
   b. **Repeated Dose Toxicity:** 2-sec-butylcyclohexanone (CAS # 14765-30-1)
   c. **Reproductive Toxicity:** 2-sec-Butylcyclohexanone (CAS # 14765-30-1)
   d. **Skin Sensitization:** 4-*t*-Amylcyclohexanone (CAS # 16587-71-6)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification**: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional references

None.

8. Natural occurrence

p-tert-Butylcyclohexanone is not reported to occur in foods 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 03/26/20 (ECHA, 2011).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for p-*tert*-butylcyclohexanone are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.027
2	Products applied to the axillae	0.0080
3	Products applied to the face/body using fingertips	0.16
4	Products related to fine fragrances	0.15
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.038
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.038
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.038
5D	Baby cream, oil, talc	0.013
6	Products with oral and lip exposure	0.088
7	Products applied to the hair with some hand contact	0.26
8	Products with significant ano-genital exposure (tampon)	0.013
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.29
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.13
10B	Aerosol air freshener	0.52
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.013

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(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	58

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For p-*tert*-butylcyclohexanone, the basis was the reference dose of 0.16 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 350 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

1. Human Health Endpoint Summaries:

11.1. Genotoxicity

Based on the current existing data and use levels, *p-tert*-butylcyclohexanone does not present a concern for genetic toxicity.

11.1.1. Risk assessment

p-tert-Butylcyclohexanone was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of *p-tert*-butylcyclohexanone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with *p-tert*-butylcyclohexanone in an unspecified solvent at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2011a). Under the conditions of the study, *p-tert*-butylcyclohexanone was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of *p-tert*-butylcyclohexanone; however, read-across can be made to 2-*tert*-butylcyclohexanone (CAS # 1728-46-7; see Section VI).

The clastogenic activity of 2-*tert*-butylcyclohexanone was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2-*tert*-butylcyclohexanone in dimethyl sulfoxide (DMSO) at concentrations up to 1543 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 400 μg/mL in the presence and absence of metabolic activation. 2-*tert*-Butylcyclohexanone did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation system (RIFM, 2017). Under the conditions of the study, 2-*tert*-butylcyclohexanone was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to *p-tert*-butylcyclohexanone.

Based on the data available, 2-*tert*-butylcyclohexanone does not present a concern for genotoxic potential, and this can be extended to *p-tert*-butylcyclohexanone.

11.1.2. Additional references

None.

11.1.3. Literature search and risk assessment completed on

05/22/20.

11.2. Repeated dose toxicity

The MOE for *p-tert*-butylcyclohexanone is adequate for the repeated dose toxicity endpoint at the current level of use.

11.2.1. Risk assessment

There are no repeated dose toxicity data on *p-tert*-butylcyclohexanone. Read-across material 2-sec-butylcyclohexanone (CAS # 14765-30-1; see Section VI) has sufficient data for the repeated dose toxicity endpoint. In an OECD 422 and GLP-compliant study, 10 Wistar Hans rats/sex/dose were fed 2-sec-butylcyclohexanone (>97% purity) orally with diet at doses of 0, 650, 2000, and 6000 ppm. Mean daily intakes of the test material at 650 ppm were 48 mg/kg/day for males and 88 mg/kg/day for females; at 2000 ppm, they were 151 mg/kg/day for males and 226 mg/kg/day for females; and at 6000 ppm were 377 mg/kg/day and 508 mg/kg/day. Dosing in male and female rats started 2 weeks prior to mating and lasted up to euthanasia in males (at least 28 days) and in females up to 13 days post-partum (about 51–56 days for females with offspring and 42 days for females without offspring). No treatment-related mortalities were observed at any dose level. Treatment-related clinical signs such as piloerection were observed in all females at 2000 ppm and in both sexes at 6000 ppm along with hunched posture in 1 male and most females from study week 3 onwards. Following week 4, there was a significant decrease in bodyweight gain in males and females at 2000 and 6000 ppm as well as a decrease in food consumption at these doses. Treatment-related effects were observed in hematology, biochemistry, organ weights, and histopathology parameters. These were considered to be secondary to weight loss and presented with low severity. Based on the observed clinical signs at doses ≥2000 ppm, the NOAEL was considered to be 650 ppm (48 mg/kg/day) for both sexes (RIFM, 2018).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 48/3 or 16 mg/kg/day.

Therefore, the *p-tert*-butylcyclohexanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-sec-butylcyclohexanone NOAEL (mg/kg/day) by the total systemic exposure for *p-tert*-butylcyclohexanone, 16/0.00034, or 47059.

In addition, the total systemic exposure to *p-tert*-butylcyclohexanone (0.34 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.2.1.1. Derivation of reference dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose of 0.16 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for *p-tert*-butylcyclohexanone was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 16 mg/kg/day by the uncertainty factor, 100 = 0.16 mg/kg/day. The lowest NOAEL was derived from read-across material 2-sec-butylcyclohexane (CAS # 14765-30-1).

*The Expert Panel for Fragrance Safety is composed of scientific and

technical experts in their respective fields. This group provides advice and guidance.

11.2.2. Additional references

ECHA, 2018a

11.2.3. Literature search and risk assessment completed on

09/03/20.

11.3. Reproductive toxicity

The MOE for *p-tert*-butylcyclohexanone is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.3.1. Risk assessment

There are no reproductive toxicity data on *p-tert*-butylcyclohexanone. Read-across material 2-sec-butylcyclohexanone (CAS # 14765-30-1; see Section VI) has sufficient reproductive toxicity data.

In an OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 10 Wistar Hans rats/sex/dose were fed diets containing 2-sec-butylcyclohexanone at doses of 0 (basal diet only), 650, 2000, or 6000 ppm (mean daily intake of 0, 48, 151, and 377 mg/kg/day for males and 0, 88, 226, and 508 mg/kg/day for females, respectively). The animals were dosed for 2-weeks prior to mating, during mating, and continued until euthanasia for males (at least 28 days) and up to 13 days after delivery for females (51–56 days for females with offspring and 42 days for females without offspring). In addition to systemic toxicity parameters, reproductive toxicity parameters were also assessed. High-dose dams exhibited statistically significant decreases in body weight and bodyweight gain, which was associated with decreased food consumption throughout the pre-mating, post-coitum, and lactation periods. Four females were not pregnant despite evidence of mating (1 control, 2 low-dose, and 1 high-dose); no abnormalities were observed in the reproductive organs. At 6000 ppm 1/10 dams had a significant change of the estrous cycle, and 6/10 were reported to have an acyclic estrous cycle. However, most of these dams had normal litters, and no abnormalities were observed in the reproductive organs that could account for the effect on estrous cyclicity. This effect was considered to be most likely a secondary effect of the bodyweight loss (and stress related to the severely reduced food consumption) in the first treatment week (when vaginal lavage samples for estrous cycle examination were collected). One mid-dose dam (with a normal litter) also exhibited an acyclic estrous cycle, which can sporadically occur as a background finding (1/316 control females, period 2015–2017). Given the low incidence of this finding (1/10 females) and in the absence of other potentially treatment-related reproductive or developmental effects at this dose, this incidence was not considered to be adverse. Statistically significant decreases in pup body weight and bodyweight gain were reported at 6000 ppm from birth (10%) and on PND 13 (30%). No other treatment-related adverse effects were reported for fertility or on the development of pups. The NOAEL for effects on fertility was considered to be 2000 ppm or 226 mg/kg/day, based on alterations in length and acyclic estrous cycle observed among the high-dose group dams. The NOAEL for developmental toxicity was considered to be 2000 ppm or 226 mg/kg/day, based on decreased pup body weight among high-dose group pups (RIFM, 2018; also available in ECHA, 2018a).

Therefore, the *p-tert*-butylcyclohexanone MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-sec-butylcyclohexanone NOAEL in mg/kg/day by the total systemic exposure to *p-tert*-butylcyclohexanone, 226/0.00034, or 664705.

In addition, the total systemic exposure to 2-cyclohexylcyclohexanone (0.34 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.3.2. Additional references

None.

11.3.3. Literature search and risk assessment completed on

05/09/20.

11.4. Skin sensitization

Based on the existing data and read-across material 4-*t*-amylcyclohexanone (CAS # 16587-71-6), *p-tert*-butylcyclohexanone is considered a skin sensitizer with a defined NESIL of 350 μg/cm^2.

11.4.1. Risk assessment

Limited skin sensitization studies are available for *p-tert*-butylcyclohexanone. Based on the existing data and read-across material 4-*t*-amylcyclohexanone (CAS # 16587-71-6; see Section VI), *p-tert*-butylcyclohexanone is considered a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly, as well as through metabolites and autoxidation products (Roberts et al., 2007; OECD Toolbox v4.2; TIMES-SS v2.28.1). In separate modified murine local lymph node assays (LLNAs), *p-tert*-butylcyclohexanone and read-across material 4-*t*-amylcyclohexanone did not induce contact sensitization up to 50% (ECHA, 2011a; ECHA, 2018b). In human maximization tests with 6% (4140 μg/cm^2) *p-tert*-butylcyclohexanone and 8% (5520 μg/cm^2) read-across material 4-*t*-amylcyclohexanone in petrolatum, no skin sensitization reactions were observed (RIFM, 1974; RIFM, 1973). In contrast, in 2 Confirmation of No Induction in Humans (CNIH) tests with 1.25% or 689 μg/cm^2 read-across material 4-*t*-amylcyclohexanone in 1:3 ethanol:diethyl phthalate (EtOH:DEP) and 2.5% (1938 μg/cm^2) of read-across material 4-*t*-amylcyclohexanone in 95% EtOH, reactions indicative of sensitization were observed in 1/100 and 1/42 volunteers, respectively (RIFM, 2012a; RIFM, 1964a). However, in 2 other CNIH tests with 0.65% (358 μg/cm^2) read-across material 4-*t*-amylcyclohexanone in 1:3 ethanol: diethyl phthalate or 1.25% (969 μg/cm^2) read-across material 4-*t*-amylcyclohexanone in 95% EtOH, no reactions indicative of sensitization were observed in any of the 108 and 41 volunteers, respectively (RIFM, 2012b; RIFM, 1964b).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and data on the read-across material 4-*t*-amylcyclohexanone, *p-tert*-butylcyclohexanone is a sensitizer with a WoE NESIL of 350 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose of 0.16 mg/kg/day.

11.4.2. Additional references

Klecak (1979); Klecak (1985).

11.4.3. Literature search and risk assessment completed on

05/08/20.

11.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *p-tert*-butylcyclohexanone would not be expected to present a concern for phototoxicity or photoallergenicity.

11.5.1. Risk assessment

There are no phototoxicity studies available for *p-tert*-butylcyclohexanone in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, *p-tert*-butylcyclohexanone does not present a

Table 1
Data summary for 4-*t*-amylcyclohexanone as read-across for *p-tert*-butylcyclohexanone.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[2] (Induction) μg/cm^2	WoE NESIL[3] μg/cm^2
NA	NA	358	5520	689	350

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2] Data derived from CNIH or HMT.
[3] WoE NESIL limited to 2 significant figures.

concern for phototoxicity or photoallergenicity.

11.5.2. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

11.5.3. Additional references

None.

11.5.4. Literature search and risk assessment completed on

05/08/20.

11.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level of *p-tert*-butylcyclohexanone is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.6.1. Risk assessment

There are no inhalation data available on *p-tert*-butylcyclohexanone. Based on the Creme RIFM Model, the inhalation exposure is 0.0033 mg/day. This exposure is 142.4 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 current level of use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

11.6.2. Additional references

None.

11.6.3. Literature search and risk assessment completed on

05/04/20.

2. Environmental Endpoint Summary:

11.7. Screening-level assessment

A screening-level risk assessment of *p-tert*-butylcyclohexanone was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, *p-tert*-butylcyclohexanone 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 v4.11 (US EPA, 2012a) identified *p-tert*-butylcyclohexanone as possibly persistent but 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 v4.11).

11.8. Risk assessment

Based on the current Volume of Use (2015), *p-tert*-butylcyclohexanone does not present a risk to the aquatic compartment in the screening-level assessment.

11.9. Key studies

11.9.1. Biodegradation

No data available.

11.9.2. Ecotoxicity

No data available.

11.10. Other available data

p-tert-Butylcyclohexanone has been registered under REACH and the following data is available (ECHA, 2011a):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. After 28 days, biodegradation of 32% was observed.

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 values based on the mean measured concentration for growth rate and biomass

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	33.61			1000000	0.03361	

were reported to be 60 mg/L and 45 mg/L, respectively.

11.10.1. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.91	2.91
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.03361 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

11.10.2. Literature search and risk assessment completed on

05/07/20.

12. Literature search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://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. The links listed above were active as of 04/21/21.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112709.

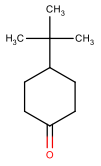
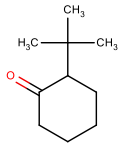
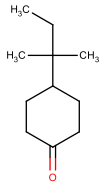
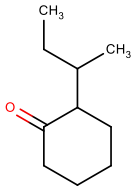
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- 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 material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using the RIFM Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	*p-tert*-Butylcyclohexanone	2-*tert*-Butylcyclohexanone	4-*t*-Amylcyclohexanone	2-sec-Butylcyclohexanone
CAS No.	98-53-3	1728-46-7	16587-71-6	14765-30-1
Structure				
Similarity (Tanimoto Score)		0.84	0.97	0.84
Endpoint		Genotoxicity	Skin sensitization	Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_{10}H_{18}O$	$C_{10}H_{18}O$	$C_{11}H_{20}O$	$C_{10}H_{18}O$
Molecular Weight	154.253	154.253	168.28	154.253
Melting Point (°C, EPI Suite)	48.50	8.41	19.58	1.92
Boiling Point (°C, EPI Suite)	210.92	210.92	229.87	218.54
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.31E+01	4.09E+01	1.61E+01	2.83E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.40E+02	2.40E+02	7.87E+01	2.23E+02
Log KOW	2.91	2.91	3.4	2.94
J_{max} (μg/cm^2/h, SAM)	17.06	17.06	7.32	16.40
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.61E+01	1.61E+01	2.14E+01	1.61E+01
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found		
Carcinogenicity (ISS)	No alert found	No alert found		
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found		
Oncologic Classification	Not classified	Not classified		
Repeated Dose Toxicity				
Repeated Dose (HESS)	Not categorized			Not categorized
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group			Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)			Toxicant (good reliability)
Skin Sensitization				
Protein Binding (OASIS v1.1)	No alert found		No alert found	
Protein Binding (OECD)	No alert found		No alert found	
Protein Binding Potency	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found		No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.		No skin sensitization reactivity domains alerts identified.	
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on *p-tert*-butylcyclohexanone (CAS # 98-53-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 2-*tert*-

butylcyclohexanone (CAS # 1728-46-7), 4-*t*-amylcyclohexanone (CAS # 16587-71-6), and 2-sec-butylcyclohexanone (CAS # 14765-30-1) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 2-*tert*-Butylcyclohexanone (CAS # 1728-46-7) was used as a read-across analog for the target material *p-tert*-butylcyclohexanone (CAS # 98-53-3) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of substituted cyclohexanones.
  - The target material and the read-across analog share a cyclohexanone substructure.
  - The key difference between the target material and the read-across analog is that the target material has a *p-tert*-butyl group while the read-across has an *o-tert*-butyl group on the ring. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - There are no alerts for the target material or the read-across analog. *In silico* alerts are consistent with data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 4-*t*-Amylcyclohexanone (CAS # 16587-71-6) was used as a read-across analog for the target material *p-tert*-butylcyclohexanone (CAS # 98-53-3) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of substituted cyclohexanones.
  - The target material and the read-across analog share a cyclohexanone substructure.
  - The key difference between the target material and the read-across analog is that the target material has a *p-tert*-butyl group, whereas the read-across material has a *p-tert*-amyl group on the ring. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - There are no alerts for the target material or the read-across analog. *In silico* alerts are consistent with data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-sec-Butylcyclohexanone (CAS # 14765-30-1) was used as a read-across analog for the target material *p-tert*-butylcyclohexanone (CAS # 98-53-3) for the repeated dose toxicity and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of substituted cyclohexanones.
  - The target material and the read-across analog share a cyclohexanone substructure.
  - The key difference between the target material and the read-across analog is that the target material has a *p-tert*-butyl group, whereas the read-across has an *o-sec*-butyl group on the ring. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - There are no alerts for the target material or the read-across analog. *In silico* alerts are consistent with data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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