Food and Chemical Toxicology 167 (2022) 113214

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol, CAS Registry Number 67634-11-1

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], M. Date [a], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], M. Na [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

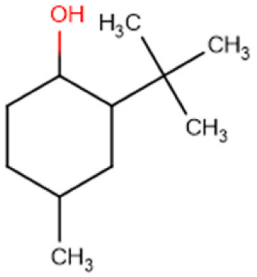
* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2022.113214
Received 14 January 2022; Received in revised form 31 May 2022; Accepted 4 June 2022
Available online 9 June 2022

Version: 011422. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: 2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol

CAS Registry Number: 67634-11-1



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., 2021)
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
ISS - Integrated Summary of Safety
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-*tert*-butylcyclohexanol (CAS # 13491-79-7) show that 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol is not expected to be genotoxic. Data on analog 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from analog *l*-menthol (CAS # 2216-51-5) show that there are no safety concerns for 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol 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 I material; exposure to 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

(*continued on next page*)

(*continued*)

Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(RIFM, 1998a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day.	JECDB (2013)
Reproductive Toxicity: Developmental toxicity NOAEL = 150 mg/kg/day. Fertility NOAEL = 500 mg/kg/day.	JECDB (2013)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(RIFM, 1995; RIFM, 2018b; RIFM, 2018a; RIFM, 1990; RIFM, 1974b)
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: Screening-level: 2.77 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 154.4 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Screening-level: Fish LC50: 5.88 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: 5.88 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00588 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** 2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol
2. **CAS Registry Number:** 67634-11-1
3. **Synonyms:** 2-*tert*-Butyl-4-methylcyclohexanol; Cyclohexanol, 2-(1,1-dimethylethyl)-4-methyl-; Idahol; 2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol
4. **Molecular Formula:** $C_{11}H_{22}O$
5. **Molecular Weight:** 170.29 g/mol
6. **RIFM Number:** 5824
7. **Stereochemistry:** Stereoisomer not specified. Three chiral centers present and a total of 8 enantiomers possible.

2. Physical data

1. **Boiling Point:** 230.26 °C (EPI Suite)
2. **Flash Point:** 89 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.83 (EPI Suite)
4. **Melting Point**: 11.75 °C (EPI Suite)
5. **Water Solubility:** 105.3 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0068 mm Hg at 20 °C (EPI Suite v4.0), 0.0114 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.14% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00029 mg/kg/day or 0.025 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0053 mg/kg/day (RIFM, 2019)

*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

6.1. Cramer classification

Class I, Low (Expert Judgment).

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

*See the Appendix below for more information.

6.2. Analogs selected

a. **Genotoxicity:** 2-*tert*-Butylcyclohexanol (CAS # 13491-79-7)
b. **Repeated Dose Toxicity:** 2-*tert*-Butylcyclohexyl acetate (CAS # 88-41-5)
c. **Reproductive Toxicity:** 2-*tert*-Butylcyclohexyl acetate (CAS # 88-41-5)
d. **Skin Sensitization:** *l*-Menthol (CAS # 2216-51-5) and weight of evidence (WoE) from menthol isomers menthol (CAS # 89-78-1), *d*-menthol (CAS # 15356-60-2), menthol racemic (CAS # 15356-70-4), and DL-isomenthol (CAS # 3623-52-7)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References:
None.

8. Natural occurrence

2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol 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

No dossier available as of 06/09/21.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. 2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014a). 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.

There are no studies assessing the mutagenic or clastogenic activity of 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol; however, read-across can be made to 2-tert-butylcyclohexanol (CAS # 13491-79-7; see Section VI).

The mutagenic activity of 2-tert-butylcyclohexanol 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 TA1538 were treated with 2-tert-butylcyclohexanol 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 concentration in the presence or absence of S9 (RIFM, 1998a). Under the conditions of the study, 2-tert-butylcyclohexanol was not mutagenic in the Ames test, and this can be extended to 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol.

The clastogenic activity of 2-tert-butylcyclohexanol 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-butylcyclohexanol in DMSO at concentrations up to 1563 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 300 μg/mL in the presence and absence of metabolic activation. 2-tert-Butylcyclohexanol did induce binucleated cells at 250 μg/mL in the 4-h treatment in the presence of an S9 activation system (RIFM, 2014b). However, this increase was within the historical control range and not dose response related, so this result was considered not biologically relevant. Under the conditions of the study, 2-tert-butylcyclohexanol was considered to be non-clastogenic in the in vitro micronucleus test, and this can be extended to 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol.

Based on the data available, 2-tert-butylcyclohexanol does not present a concern for genotoxic potential, and this can be extended to 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol.

Additional References: RIFM, 1998b; RIFM, 2014a.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data for 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol. Read-across material, 2-tert-butylcyclohexyl acetate (CAS # 88-41-5; see Section VI), has sufficient repeated dose toxicity data. A gavage combined repeated dose toxicity study and reproduction/developmental toxicity screening test was conducted in Sprague Dawley SPF rats. Groups of 12 rats/sex/dose were administered 0, 50, 150, or 500 mg/kg/day 2-tert-butylcyclohexyl acetate in a corn oil vehicle daily for 14 days before mating, through the mating period, until the day of necropsy for males (day of study 42) and through gestation and 4 days of lactation for the females (day of study 41–46). Additional non-mating satellite groups of 10 female rats/dose were administered 0 or 500 mg/kg/day for 42 days. From these groups, 5 rats/sex/dose from the mating groups were gavaged with 0 or 500 mg/kg/day, and 5 and 3 non-mating satellite female rats were gavaged with 0 and 500 mg/kg/day, respectively, for the 42 days described above then maintained for a further 14-day treatment-free recovery period. At 500 mg/kg/day, mortality occurred in 4 mating group females and 3 non-mating group females. At 500 mg/kg/day in both sexes, adverse clinical signs (salivation and/or clonic convulsions), reduced body-weight gain, decreased food consumption, and changes in urinalysis, clinical chemistry, and/or hematology were observed. Increased liver weights were observed in males at concentrations ≥50 mg/kg/day and females at concentrations ≥150 mg/kg/day; centrilobular hepatocyte hypertrophy was observed at concentrations ≥150 mg/kg/day in both sexes. Increased thyroid weights were observed in females at 500 mg/kg/day; hypertrophy of thyroid follicular epitheliocytes was observed in males at concentrations ≥150 mg/kg/day and females at 500 mg/kg/day. Increased kidney weights were observed in males at concentrations ≥50 mg/kg/day; acidophilic corpuscles of the kidney tubular epitheliocytes were observed in males at concentrations ≥50 mg/kg/day, regenerated uriniferous tubules in males at concentrations ≥150 mg/kg/day, and dilation of uriniferous tubules, granular casts, and cell infiltration the interstitium in males at 500 mg/kg/day. Immunohistochemical staining of the kidneys from male rats was positive for α-2u-globulin. While increased kidney weights were observed in females at concentrations ≥150 mg/kg/day, there were no accompanying histopathological changes. Increased adrenal weights were observed in females at concentrations ≥150 mg/kg/day; vacuolization of the epithelial cells was observed at 500 mg/kg/day. Decreased thymus weights were observed in females at 500 mg/kg/day. All effects observed were improved or disappeared following the recovery period, with the exception of kidney changes (regenerated uriniferous tubules, granular casts, increased urinary output, and increased chloride excretion). The kidney changes in the male rats were attributed to α-2u-globulin nephropathy, a male rat-specific phenomenon that is not

indicative of a hazard to human health. The increased liver weights observed in male rats at 50 mg/kg/day were not accompanied by any histopathological changes, and the liver effects observed at 500 mg/kg/day were shown to decrease in severity and frequency after the recovery period, suggesting recoverability. The NOAEL for repeated dose toxicity selected for this safety assessment was determined to be 50 mg/kg/day, based on centrilobular hepatocyte hypertrophy seen in mid- and high-dose groups (JECDB, 2013).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 50/3 or 16.67 mg/kg/day.

Therefore, the 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-tert-butylcyclohexyl acetate NOAEL in mg/kg/day by the total systemic exposure to 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol, 16.67/0.0053, or 3145.

In addition, the total systemic exposure to 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol (5.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/02/21.

11.1.3. Reproductive toxicity

The MOE for 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol. Read-across material, 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5; see Section VI) has sufficient reproductive toxicity data. A gavage combined repeated dose toxicity study and reproduction/developmental toxicity screening test was conducted in Sprague Dawley SPF rats. Groups of 12 rats/sex/dose were administered 0, 50, 150, or 500 mg/kg/day 2-*tert*-butylcyclohexyl acetate in a corn oil vehicle daily for 14 days before mating, through the mating period, until the day of necropsy for males (day of study 42) and through gestation and 4 days of lactation for the females (day of study 41–46). Additional non-mating satellite groups of 10 female rats/dose were administered 0 or 500 mg/kg/day for 42 days. From these groups, 5 rats/sex/dose from the mating groups were gavaged with 0 or 500 mg/kg/day, and 5 and 3 non-mating satellite female rats were gavaged with 0 and 500 mg/kg/day, respectively, for the 42 days described above then maintained for a further 14-day treatment-free recovery period. At 500 mg/kg/day, mortality occurred in 4 mating group females and 3 non-mating group females. At 500 mg/kg/day in both sexes, adverse clinical signs (salivation and/or clonic convulsions), reduced bodyweight gain, decreased food consumption, and changes in urinalysis, clinical chemistry, and/or hematology were observed. No effects on fertility were observed in P generation males or females. Decreased pup bodyweight gain from postnatal days 0–4 in pups from the 500 mg/kg/day group was observed. The NOAEL for fertility in the parental generation was determined to be 500 mg/kg/day, the highest dose tested, and the NOAEL for the developmental toxicity was determined to be 150 mg/kg/day (JECDB, 2013).

Therefore, the 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol MOE for the developmental toxicity endpoint can be calculated by dividing the 2-*tert*-butylcyclohexyl acetate NOAEL in mg/kg/day by the total systemic exposure to 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol, 150/0.0053, or 28302.

The 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol MOE for the fertility endpoint can be calculated by dividing the 2-*tert*-butylcyclohexyl acetate NOAEL in mg/kg/day by the total systemic exposure to 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol, 500/0.0053, or 94340.

In addition, the total systemic exposure to 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol (5.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/02/21.

11.1.4. Skin sensitization

Based on the existing data and the read-across material *l*-menthol (CAS # 2216-51-5) and WoE from menthol isomers (menthol, CAS # 89-78-1; *d*-menthol, CAS # 15356-60-2; menthol racemic, CAS # 15356-70-4; DL-isomenthol, CAS # 3623-52-7), 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the available data, read-across material *l*-menthol (CAS # 2216-51-5; see Section VI) and WoE from menthol isomers (menthol, CAS # 89-78-1; *d*-menthol, CAS # 15356-60-2; menthol racemic, CAS # 15356-70-4), 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). WoE material DL-isomenthol was found to be negative in an in vitro KeratinoSens and human cell line activation test (h-CLAT) (RIFM, 2018b; RIFM, 2018a). In a murine local lymph node assay (LLNA), read-across material *l*-menthol was not sensitizing up to the highest tested concentration of 30% (7500 μg/cm^2) (RIFM, 1995). In guinea pig sensitization tests, including a Buehler test and an open epicutaneous test, no reactions indicative of sensitization were observed with read-across materials, l-menthol, and menthol isomers (Brazilian, racemic, *l*-menthol, *d*-menthol) (RIFM, 1990; RIFM, 1974b). In another guinea pig study conducted according to the modified Draize procedure, a positive response was reported for read-across l-menthol only after the same animals were re-tested utilizing the full induction and challenge procedure (Sharp, 1978). This result is not considered to be of significance as the test was not conducted on naïve animals (Sharp, 1978; ECHA, 2012). Furthermore, in 2 separate human maximization tests, no skin sensitization reactions were observed when conducted using 8% (5520 μg/cm^2) of read-across l-menthol and menthol racemic, respectively (RIFM, 1974a; RIFM, 1973a). In a Confirmation of No Induction in Humans (CNIH) test, 194 μg/cm^2 of 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol in SDA 39C, did not produce reactions indicative of sensitization in any of the 43 volunteers (RIFM, 1973b).

Based on the WoE from structural analysis and a human study and read-across material *l*-menthol and WoE materials menthol isomers, 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: Valosen et al., 1999; Ishihara et al., 1986; Xu et al., 2006; Friedrich et al., 2007.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. The available UV/Vis spectra for 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol indicate no absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxic effects. Based on the

lack of absorbance in the critical range and benchmark evaluation, 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available UV/Vis spectra (OECD TG 101) for 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol indicate no absorbance between 290 and 700 nm. The molar absorption coefficient for λ max between 290 and 700 nm is below the benchmark of concern for phototoxicity, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The inhalation exposure for 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol is below the TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol. Based on the Creme RIFM Model, the inhalation exposure is 0.025 mg/kg/day. This exposure is 56 times lower than the TTC for a Cramer Class I material (0.023 mg/kg/day; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol 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, 2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol 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) did not identify 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol has been pre-registered for REACH with no additional data at this time.

11.2.3. 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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>14.52</u>			1000000	0.01452	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.83	3.83
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.00588 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 05/17/21.

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 01/14/22.

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.2022.113214.

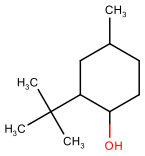
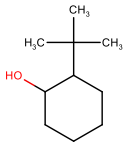
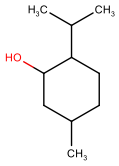
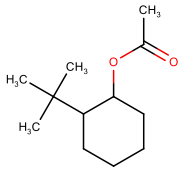
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). These criteria follow 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 RIFM's 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 material 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 choice of the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	2-(1,1-Dimethylethyl)-4-methylcyclohexan-1-ol	2-*tert*-Butylcyclohexanol	*l*-Menthol	2-*tert*-Butylcyclohexyl acetate
CAS No.	67634-11-1	13491-79-7	2216-51-5	88-41-5
Structure				
Similarity (Tanimoto Score)		0.97	0.94	0.49
SMILES	CC1CCC(O)C(C1)C(C)(C)C	CC(C)(C)C1CCCCC1O	CC(C)C1CCC(C)CC1O	CC(=O)OC1CCCCC1C(C)(C)C
Endpoint		Genotoxicity	Skin sensitization	Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_{11}H_{22}O$	$C_{10}H_{20}O$	$C_{10}H_{20}O$	$C_{12}H_{22}O_2$
Molecular Weight (g/mol)	170.296	156.269	156.269	198.306
Melting Point (°C, EPI Suite)	11.75	45.00	79.50	34.50
Boiling Point (°C, EPI Suite)	230.26	216.91	216.00	232.55
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.52E+00	2.11E+00	8.49E+00	7.11E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.05E+02	2.78E+02	4.90E+02	7.46E+00
Log K_{OW}	3.83	3.42	3.19	4.42
J_{max} (μg/cm^2/h, SAM)	13.34	31.49	45.30	0.98
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.05E+00	1.54E+00	1.54E+00	1.00E+02
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)	Moderate binder, OH group			Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)			Toxicant (moderate 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 domain alerts identified.		No skin sensitization reactivity domain 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 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol (CAS # 67634-11-1). 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*-butylcyclohexanol (CAS # 13491-79-7), *l*-menthol (CAS # 2216-51-5), and 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the read-across analog 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol (CAS # 67634-11-1) and acetic acid (CAS # 64-19-7) in the first step with 95% probability. Hence, 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) can be used as a read-across analog for the target material. Read-across analog was in domain for the *in vivo* and in vitro rat S9 simulator (OASIS TIMES v2.27.19).

Conclusions

- 2-*tert*-Butylcyclohexanol (CAS # 13491-79-7) was used as a read-across analog for the target material 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol (CAS # 67634-11-1) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of substituted cyclohexanols.
  - o The key difference between the target material and the read-across analog is that the target material has methyl substitution at 4 position, which the read-across analog lacks. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no alerts for the target material and the read-across analog. Therefore, the absence of *in silico* alerts is consistent with data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- *l*-Menthol (CAS # 2216-51-5) was used as a read-across analog for the target material 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol (CAS # 67634-11-1) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of substituted cyclohexanols.
  - o The key difference between the target material and the read-across analog is that the target material has a methyl substitution at the 4 position and a tertiary butyl substitution at the 2 position, whereas the read-across analog has a methyl substitution at the 5 position and an isopropyl substitution at the 2 position. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no alerts for the target material and the read-across analog. Therefore, the absence of *in silico* alerts is consistent with data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-*tert*-Butylcyclohexyl acetate (CAS # 88-41-5) was used as a read-across analog for the target material 2-(1,1-dimethylethyl)-4-methylcyclohexan-1-ol (CAS # 67634-11-1) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of substituted cyclohexanols.
  - o The key difference between the target material and the read-across analog is that the target material has a methyl substitution at the 4 position and a tertiary butyl substitution at the 2 position, while the read-across analog has a methyl substitution at the 5 position and an isopropyl substitution at the 2 position. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have an alert of being Toxicant by the CAESAR model for developmental toxicity. The data on the read-across analog confirms that the MOE is adequate at the current level of use for systemic endpoints. Therefore, the absence of *in silico* alerts is consistent with data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

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

Q1.Normal constituent of the body? No.
Q2.Contains functional groups associated with enhanced toxicity? No.
Q3.Contains elements other than C,H,O,N, divalent S? No.
Q5.Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6.Benzene derivative with certain substituents? No.
Q7.Heterocyclic? No.
Q16.Common terpene? No.
Q17.Readily hydrolyzed to a common terpene? No.
Q19.Open chain? No.
Q23.Aromatic? No.
Q24.Monocarbocyclic with simple substituents? Yes.

Q18.One of the list (see explanation in Cramer et al., 1978)? No Class Low (Class I).

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

ECHA, 2012. Guidance on information requirements and chemical safety assessment, November 2012 v2.1. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment. (Accessed 14 January 2022).

ECHA, 2017. Read-across assessment framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a. (Accessed 14 January 2022).

Friedrich, K., Delgado, I.F., Santos, L.M.F., Paumgartten, F.J.R., 2007. Assessment of sensitization potential of monoterpenes using the rat popliteal lymph node assay. Food Chem. Toxicol. 45 (8), 1516–1522.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Ishihara, M., Itoh, M., Nishimura, M., Kinoshita, M., Kantoh, H., Nogami, T., Yamada, K., 1986. Closed epicutaneous test. Skin Res. 28 (Suppl. 2), 230–240.

Japan Existing Chemical Data Base (JECDB), 2013. Combined Repeated Does Toxicity and Reproductive/developmental Toxicity Study by Oral Administration of 2-Tert-Butylcyclohexane-1-Yl-Acetate to Rats. Online Publication.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. https://one.oecd.org/document/ENV/JM/HA(2015)7/en/pdf. (Accessed 14 January 2022).

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/. (Accessed 14 January 2022).

RIFM (Research Institute for Fragrance Materials, Inc.), 1973a. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1802.

RIFM (Research Institute for Fragrance Materials, Inc.), 1973b. Repeated Insult Patch Test with 2-(1,1-Dimethylethyl)-4-Methylcyclohexan-1-Ol. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 52649.

RIFM (Research Institute for Fragrance Materials, Inc.), 1974a. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1801.

RIFM (Research Institute for Fragrance Materials, Inc.), 1974b. Eye and Skin Irritation with Brazilian Menthol (Peppermint Oil), Racemic 100 Menthol, L-Menthol, and D-Menthol. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 54867.

RIFM (Research Institute for Fragrance Materials, Inc.), 1990. l-Menthol: Buehler Sensitization Test in guinea Pigs. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 54871.

RIFM (Research Institute for Fragrance Materials, Inc.), 1995. l-Menthol: Local Lymph Node Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 54874.

RIFM (Research Institute for Fragrance Materials, Inc.), 1998. 2-tert-Butylcyclohexanol: Reverse Mutation in Salmonella typhimurium. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 62123.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Report on the Testing of 2-(1,1-Dimethylethyl)-4-Methylcyclohexan-1-Ol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 67258.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. 2-tert-Butylcyclohexanol (Verdol): Micronucleus Test in Human Lymphocytes in Vitro. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 67365.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018a. Menthol and DL-Isomenthol (Reaction Mass of (1S, 2R, 5R)-Rel-5-Methyl-2-(1-Methylethyl)-Cyclohexan-1-Ol and DL-Menth) (Menthol Iso rac.): in Vitro Skin Sensitization Test - Human Cell Line Activation Test (H-CLAT). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 74775.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018b. Menthol and DL-Isomenthol (Reaction Mass of (1S, 2R, 5R)-Rel-5-Methyl-2-(1-Methylethyl)-Cyclohexan-1-Ol and DL-Menth) (Menthol Iso rac.): in Vitro Skin Sensitization ARE-Nrf2 Luciferase Test Method (KeratinoSense). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 74802.

RIFM (Research Institute for Fragrance Materials, Inc.), 2019. Exposure Survey 24, March 2019.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76272.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Sharp, D.W., 1978. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9 (3), 261–271.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.

Valosen, J.M., Hayes, B.B., Howell, M.D., Manetz, T.S., Woolhiser, M.R., Meade, B.J., 1999. Evaluation of human irritants and weak to moderate sensitizers using a modified LLNA and an irritancy/phenotyping assay. Toxicologist 48 (1-S), 313.

Xu, H., Delling, M., Jun, J.C., Clapham, D.E., 2006. Oregano, thyme and clove-derived flavors and skin sensitizers activate specific TRP channels. Nat. Neurosci. 9 (5), 628–635.