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RIFM fragrance ingredient safety assessment, 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol, CAS Registry Number 139504-68-0

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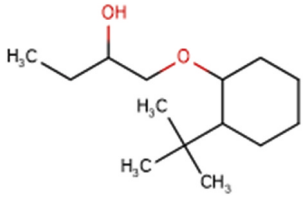

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Name: 1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol
CAS Registry Number: 139,504-68-0

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

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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 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.

1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol is not genotoxic. Data on 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Based on the existing data and read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexanol (CAS # 70,788-30-6), 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol is a skin sensitizer with a defined No Expected Sensitization Induction Level (NESIL) of 3100 μg/cm^2. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol 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 III material, and the exposure to 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (ECHA REACH Dossier: 1-[(2-tert-Butylcyclohexyl)oxy] butan-2-ol; ECHA, 2012a)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day. (ECHA REACH Dossier: 1-[(2-tert-Butylcyclohexyl)oxy]butan-2-ol; ECHA, 2012a)
Reproductive Toxicity: NOAEL = 500 mg/kg/day. (ECHA REACH Dossier: 1-[(2-tert-Butylcyclohexyl)oxy]butan-2-ol; ECHA, 2012a)
Skin Sensitization: NESIL = 3100 μg/cm^2 (RIFM, 2017)
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: 5% (OECD 301C)	(ECHA REACH Dossier: 1-[(2-tert-Butylcyclohexyl)oxy]butan-2-ol; ECHA, 2012a)

Bioaccumulation:

Critical Measured Value: BCF: 173 (OECD 305C)	(ECHA REACH Dossier: 1-[(2-tert-Butylcyclohexyl)oxy]butan-2-ol; ECHA, 2012a)

Ecotoxicity:

Critical Ecotoxicity Endpoint: 33-Day Fathead minnow NOEC: 0.22 mg/L	(ECHA REACH Dossier: 1-[(2-tert-Butylcyclohexyl)oxy]butan-2-ol; ECHA, 2012a)

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: 33-Day Fathead minnow NOEC: 0.22 mg/L	(ECHA REACH Dossier: 1-[(2-tert-Butylcyclohexyl)oxy]butan-2-ol; ECHA, 2012a)

RIFM PNEC is: 22 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: <1

1. Identification

1. **Chemical Name:** 1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol
2. **CAS Registry Number:** 139,504-68-0
3. **Synonyms:** 1-(2-*tert*-ﾌﾞﾁﾙｼｸﾛﾍｷｼﾙｵｷｼ)-2-ﾌﾞﾀﾉｰﾙ; AmberCore; 1-(2-*tert*.-Butyl cyclohexyloxy)-2-butanol
4. **Molecular Formula:** $C_{14}H_{28}O_2$
5. **Molecular Weight:** 228.37
6. **RIFM Number:** 6523
7. Stereochemistry:

2. Physical data

1. **Boiling Point:** 292.87 °C (EPI Suite)
2. **Flash Point:** 132 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.05 (KOWWIN v1.68 in EPI Suite)
4. **Melting Point**: 52.67 °C (EPI Suite)
5. **Water Solubility:** 34.85 mg/L at 25 °C (WSKOW v1.42 in EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000579 mm Hg at 20 °C (EPI Suite v4.0)
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. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.79% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00072 mg/kg/day or 0.050 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 40%

Name	1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol
J_{max} (mg/cm^2/h)	0.0098[1]
Skin Absorption Class	40%

[1] J_{max} was calculated based on estimated log K_{OW} = 4.29 (consensus model) and Solubility = 161 mg/L (consensus model).

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class III, High

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

6.2. Analogs Selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 1-(2,2,6-Trimethylcyclohexyl)-3-hexanol (CAS # 70,788-30-6)
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

1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol 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 09/22/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol 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)	0.24
2	Products applied to the axillae	0.071
3	Products applied to the face/body using fingertips	1.4
4	Products related to fine fragrances	1.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.34
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.34
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.34
5D	Baby cream, oil, talc	0.11
6	Products with oral and lip exposure	0.75
7	Products applied to the hair with some hand contact	2.7
8	Products with significant ano-genital exposure (tampon)	0.11
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.6
10A	Household care products with mostly hand contact (hand dishwashing detergent)	4.5
10B	Aerosol air freshener	9.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.11
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

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 1-(2-tert-butyl cyclohexyloxy)-2-butanol, the basis was the reference dose of 5 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 3100 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).
cCalculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA, 2012a). Under the conditions of the study, 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol was not mutagenic in the Ames test.

The clastogenic activity of 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in sodium chloride (0.9% w/v) via intraperitoneal injection to groups of male HSD:ICR mice. Doses of 500, 1000, or 2000 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2012a). Under the conditions of the study, 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/09/21.

11.1.2. Repeated dose toxicity

The MOE for 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol. In a GLP compliant toxicity study, 6 Crj:CD (SD) rats/sex/dose were administered 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol at doses of 0, 20, 140, or 1000 mg/kg/day in a 0.5% sodium carboxymethylcellulose/Tween 80 vehicle for 28 days through oral gavage. In addition, 6 rats/sex/dose were added to the control and high-dose groups to serve as the 14-day treatment-free recovery groups. Both absolute and relative liver weights among the high-dose group animals were increased; this effect was also observed among the recovery-group animals. In addition, the recovery-group males also had an increase in relative kidney weights compared to the controls. During necropsy, treatment groups showed a brownish color of the liver in animals of the high-dose group and renal discoloration in males of the mid- and high-dose groups. Male kidney discoloration was also seen in the recovery-group animals. Microscopic changes in the kidney included hyaline droplets in the tubular epithelium in control and treated males. Diffuse hypertrophy of hepatocytes was reported in high-dose group animals, and the cytoplasm of the affected hepatocytes appeared eosinophilic and granular; this change was not observed in animals examined after the recovery period. Bile pigments in hepatocytes and connective tissues were reported among the high-dose group animals. Bile plugs in the intralobular bile duct (cholestasis) and cholangitis, which consisted mainly of lymphocytic infiltration, were found in high-dose group males; this was also seen in the recovery-group animals. Kidney changes reported in males were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health. Since the liver weight increases were associated with cholangitis, which consisted mainly of lymphocytic infiltration (inflammation), this alteration was considered to be toxicologically relevant. Thus, the NOAEL was considered to be 140 mg/kg/day (ECHA, 2012a).

In an OECD 415/GLP 1-generation reproductive toxicity study, groups of 24 Wistar rats/sex/dose were administered 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol via gavage at doses of 0, 20, 100, or 500 mg/kg/day in a 0.5% sodium carboxymethylcellulose/Tween 80 vehicle. The males were treated for at least 10 weeks prior to pairing and continued until termination (at least 18 weeks of treatment), and the females were treated for at least 2 weeks prior to pairing and throughout mating, gestation, and lactation until weaning (day 21 of lactation). Absolute and relative liver weights in both sexes were increased in animals of the high-dose group, and males of the mid-dose group. The absolute and relative kidney weights among high-dose group males were also increased. The absolute pituitary gland weights were significantly lower for males than the controls; however, due to the lack of a dose response relationship and histopathological alterations, this was not considered to be of toxicological relevance. Prostate weights, both absolute and relative, were lower than the controls; however, due to the lack of associated histopathological alterations, the effect was not considered adverse. Histopathological alterations among high-dose group animals included treatment-related centrilobular hepatocyte enlargement, a greater incidence and severity of globular accumulations of eosinophilic material in the tubular epithelium of males, and treatment-related tubular necrosis in the affected isolated tubules in the outer medulla immediately adjacent to the renal cortex. Due to the lack of related alterations in the clinical chemistry parameters of necrosis of the hepatocytes, the alterations in the liver weights were considered to be treatment-related but of adaptive nature and not adverse. Kidney changes in males at 500 mg/kg/day were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and caudill, 1992; Lehman-McKeeman et al., 1990; ECHA, 2012a). The NOAEL was considered to be 500 mg/kg/day, the highest dose tested.

Since there was no dose tested between 140 and 1000 mg/kg/day in the 28-day study, and the NOAEL from the longer duration 1-generation study was 500 mg/kg/day, the NOAEL for repeated dose toxicity endpoint was considered to be 500 mg/kg/day.

Therefore, the 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the NOAEL in mg/kg/day by the total systemic exposure, 500/0.0053 or 94,340.

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, 2020) and a reference dose (RfD) of 5 mg/kg/day.

Derivation of RfD:

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 RfD for 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 500 mg/kg/day by the uncertainty factor, 100 = 5 mg/kg/day.

Additional References: None.

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

11.1.3. Reproductive toxicity

The MOE for 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol is adequate for

the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol. In an OECD 415/GLP 1-generation reproductive toxicity study, groups of 24 Wistar rats/sex/dose were administered 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol via oral gavage at doses of 0, 20, 100, or 500 mg/kg/day in a 0.5% sodium carboxymethylcellulose/Tween 80 vehicle. Males were treated for at least 10 weeks prior to pairing, and treatment continued until termination (at least 18 weeks of treatment). Females were treated for at least 2 weeks prior to pairing and then throughout mating, gestation, and lactation until weaning (day 21 of lactation). In addition to systemic toxicity parameters, the reproductive toxicity parameters were also assessed. There were no treatment-related adverse effects on fertility or on the survival, growth, or development of offspring up to the highest dose tested. The NOAEL for reproductive toxicity was considered to be 500 mg/kg/day (ECHA, 2012a).

Therefore, the 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol MOE for the reproductive toxicity endpoint can be calculated by dividing the 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol NOAEL in mg/kg/day by the total systemic exposure to 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol, 500/0.0053 or 94,340.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.4. Skin sensitization

Based on the existing data and read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexanol (CAS # 70,788-30-6), 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol is a skin sensitizer with a defined NESIL of 3100 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol. Based on the existing data and read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexanol (CAS # 70,788-30-6; see Section VI), 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol is a skin sensitizer with a defined NESIL of 3100 μg/cm^2. The chemical structure of these materials indicates that they would not be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.2; Toxtree v3.1.0). No *in chemico* or *in vitro* predictive skin sensitization studies are available for read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexanol. In a murine local lymph node assay (LLNA) BrdU-ELISA, read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexanol was found to be sensitizing with an EC1.6 value of 12.73% (3182 μg/cm^2) (RIFM, 2017). In guinea pigs, a Buehler test with read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexano did not present reactions indicative of sensitization (RIFM, 1977). In a human maximization test, no skin sensitization reactions were observed in 22 subjects conducted with 10% (6900 μg/cm^2) read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexanol (RIFM, 1985). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 2% of read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexanol in petrolatum, no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1984). In another CNIH, no reactions indicative of sensitization were observed in any of the 110 volunteers with 2.7% (3188 μg/cm^2) read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexanol in 1:3 EtOH:DEP (RIFM, 2017).

Based on the available data on read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexanol, summarized in Table 1, 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol is considered to be a weak skin sensitizer with a defined NESIL of 3100 μg/cm^2. 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, 2020) and a reference dose of 5 mg/kg/day.**

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, 1-(2-tert-Butyl cyclohexyloxy)-2-butanol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no 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).

Additional References: None.

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

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol. Based on the Creme RIFM Model, the inhalation exposure is 0.050 mg/day. This exposure is 9.4 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

Table 1
Data summary for read-across material 1-(2,2,6-trimethylcyclohexyl)-3-hexanol.

LLNA Weighted Mean EC1.6 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
3182.5 [1]	Weak	3188	6900	NA	3100

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 2significant figures.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol 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, 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol 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, 2012b). 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol presents 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. 1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol has been registered under REACH and the following data is available (ECHA, 2012a):

A ready biodegradation study was conducted according to the OECD 301C method. After 28 days, biodegradation of 5% was observed.

A fish (Carp) bioaccumulation study was conducted according to the OECD 305C method under flow-through conditions. The BCF was reported to be 173.

A 96-h fish (Rainbow trout) acute toxicity study was conducted according to the OECD 203 method under flow-through conditions. The LC50 of 4.1 mg/L based on measured concentration was reported.

A fish (Fathead minnow) Early Life Stage toxicity study was conducted according to the OECD 210 method under flow-through conditions. The 33-day NOEC based on measured concentration was reported to be 0.22 mg/L.

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 based on measured concentration was reported to be 5.9 mg/L.

A *Daphnia magna* prolonged exposure test was conducted according to the OECD 202 Part 2 guidelines under semi-static conditions. The 21-day NOEC based on mean measured concentration was reported to be 1.4 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 and NOEC (both based on growth rate) were reported to be 12 mg/L and 1.5 mg/L, respectively. The results were reported based on mean measured concentration.

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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.05	4.05
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 22 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: 06/28/21.

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 09/22/21.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	5.078			1000000	0.005078	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	2.697	1.851	3.017	10000	0.1851	Neutral Organic
Tier 3: Measured Data including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	4.1		0.22	10	22	
Daphnia		5.9	1.4			
Algae		12	1.5			

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.2021.112714.

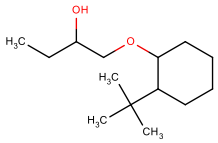
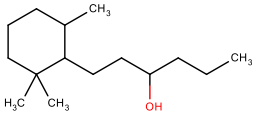
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization 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).

	Target Material	Read-across Material
Principal Name	1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol	1-(2,2,6-Trimethylcyclohexyl)-3-hexanol
CAS No.	139,504-68-0	70,788-30-6
Structure		
Similarity (Tanimoto Score)		0.45
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_{14}H_{28}O_2$	$C_{15}H_{30}O$
Molecular Weight	228.37	226.40
Melting Point (°C, EPI Suite)	52.67	56.43
Boiling Point (°C, EPI Suite)	292.87	295.02
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.0158	0.0127
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.05	5.80
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	34.85	1.149
J_{max} (μg/cm^2/h, SAM)	9.80	1.58
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.22E-002	6.35E+000
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 alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol (CAS # 139,504-68-0). 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, 1-(2,2,6-trimethylcyclohexyl)-3-hexanol (CAS # 70,788-30-6) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 1-(2,2,6-Trimethylcyclohexyl)-3-hexanol (CAS # 70,788-30-6) was used as a read-across analog for the target material 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol (CAS # 139,504-68-0) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of saturated alkyl secondary alcohols bearing a cyclohexane ring.
  - o The target material and the read-across analog share an alkyl straight chain secondary alcohol and a cyclohexane ring.
  - o The key difference between the target material and the read-across analog is that the target material has an ether group. The target material has a *tert*-butyl substitution in the cyclohexyl ring while the read-across analog has 3 methyl groups in positions 2, 2, and 6 on the cyclohexyl ring. The length of the alkyl saturated straight chain bearing the secondary alcohol group is different for both materials, i.e. a C4 chain for the target material and a C6 for the read-across analog. These structural differences are toxicologically insignificant.
  - o 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 comparison of their toxicological properties.
  - o Data are consistent with *in silico* alerts.
  - 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.

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