Food and Chemical Toxicology 127 (2019) S1–S9

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, cyclohexanol,4-(3-methylbutyl)-, CAS Registry Number 830322-14-0

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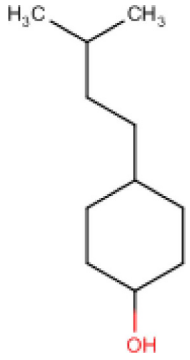
Version: 091218. This version replaces any previous versions.
Name: Cyclohexanol,4-(3-methylbutyl)-
CAS Registry Number: 830322-14-0



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https://doi.org/10.1016/j.fct.2018.11.051
Received 14 September 2018; Accepted 22 November 2018
Available online 28 November 2018
0278-6915/

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
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 under the limits described in this safety assessment.

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

Each endpoint discussed in this safety assessment 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 use of this material under current conditions is supported by existing information.

Cyclohexanol,4-(3-methylbutyl)- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cyclohexanol,4-(3-methylbutyl)- is not genotoxic. Data on read-across analogs *l*-menthol (CAS # 2216-51-5) and *d,l*-menthol (isomer unspecified; CAS # 1490-04-6) provide a calculated MOE > 100 for the repeated dose toxicity endpoint. Data on read-across analogs menthol (CAS # 89-78-1) and *d,l*-menthol (isomer unspecified; CAS # 1490-04-6) provide a calculated MOE > 100 for the developmental toxicity endpoint. The fertility and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to cyclohexanol,4-(3-methylbutyl)- is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from the target and read-across analog 4-isopropylcyclohexanol (CAS # 4621-04-9) do not indicate the material is a sensitizer. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; cyclohexanol,4-(3-methylbutyl)- is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cyclohexanol,4-(3-methylbutyl)- was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2007a; RIFM, 2009)
Repeated Dose Toxicity: NOAEL = 300 mg/kg/day. NCI (1979)
Reproductive Toxicity: Developmental Toxicity NOAEL = 425 mg/kg/day. Fertility: No NOAEL available. Exposure is below the TTC. FDA (1973)
Skin Sensitization: Data do not indicate sensitization. RIFM (2012)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 8% (OECD 301F) RIFM (2007d)
Bioaccumulation: Screening-level: 186 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 4.612 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: 4.612 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.004612 µg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Cyclohexanol,4-(3-methylbutyl)-
2. **CAS Registry Number:** 830322-14-0
3. **Synonyms:** Symrose; Cyclohexanol,4-(3-methylbutyl)-
4. **Molecular Formula:** $C_{11}H_{22}O$
5. **Molecular Weight:** 0
6. **RIFM Number:** 7305
7. **Stereochemistry:** Two stereocenters present and 4 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 242–245 °C at atmospheric pressure (1013.3 hPa) (RIFM, 2007b)
2. **Flash Point:** Not Available
3. **Log K_{ow}:** Not Available
4. **Melting Point:** −21 °C (RIFM, 2007b)
5. **Water Solubility:** Not Available
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 1.5 × 10(-2) p/Pa @ 20 °C (RIFM, 2007b), 4.3 × 10(-2) p/Pa @ 25 °C (RIFM, 2007b), 2.4 × 10(0) p/Pa @ 50 °C (RIFM, 2007b)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.38% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00096 mg/kg/day or 0.066 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.011 mg/kg/day (RIFM, 2017)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** I (Expert Judgment)

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

*Due to potential discrepancies between 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. See Appendix for explanation.

2. **Analogs Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** *l*-Menthol (CAS # 2216-51-5); *d,l*-menthol (isomer unspecified; CAS # 1490-04-6)
   c. **Reproductive Toxicity:** Menthol (CAS # 89-78-1); *d,l*-menthol (isomer unspecified; CAS # 1490-04-6)
   d. **Skin Sensitization:** 4-isopropylcyclohexanol (CAS # 4621-04-9)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-Across Justification:** See Appendix below

6. Metabolism

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

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

Cyclohexanol,4-(3-methylbutyl)- 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.

8. IFRA standard

None.

9. REACH dossier

No dossier available as of 04/20/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, cyclohexanol,4-(3-methylbutyl)- does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of cyclohexanol,4-(3-methylbutyl)- 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 pre-incubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with cyclohexanol,4-(3-methylbutyl)- 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, 2007a). Under the conditions of the study, cyclohexanol, 4-(3-methylbutyl)- was not mutagenic in the Ames test.

The clastogenicity of cyclohexanol,4-(3-methylbutyl)- was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with cyclohexanol,4-(3-methylbutyl)- in DMSO at concentrations up to 1703 μg/mL in a dose range finding (DRF) study. Micronuclei analysis in the main study was

conducted up to 159.6 μg/mL in the presence and absence of metabolic activation for 4 and 24 h. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test item, either with or without S9 metabolic activation (RIFM, 2009). Under the conditions of the study, cyclohexanol, 4-(3-methylbutyl)- was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, cyclohexanol,4-(3-methylbutyl)- does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/09/2018.

10.1.2. Repeated dose toxicity

The margin of exposure for cyclohexanol,4-(3-methylbutyl)- is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on cyclohexanol,4-(3-methylbutyl)-. Read-across materials, *l*-menthol (CAS # 2216-51-5; see Section V) and *d,l*-menthol (isomer unspecified; CAS # 1490-04-6; see Section V) have sufficient repeated dose toxicity data. In an OECD 407/GLP repeated dose toxicity study, groups of 10 rats/sex/dose were administered *l*-menthol (CAS # 2216-51-5) at doses of 0 (soybean oil), 200, 400, and 800 mg/kg/day. There was an increase in absolute and relative liver weight among all of the treated males and females at ≥400 mg/kg/day as compared to the controls. Histopathological examination revealed vacuolation of the hepatocytes among the treated animals; however, there was no dose response. The report did not mention the magnitude of liver weight increases among treated the animals. Hence, the significance of liver weight alterations could not be determined. OECD SIDS (2003) cites an unpublished report submitted to JECFA that states "no adverse effects on weight gain, excretion of glucuronides, water, or electrolytes, or interference with central nervous system reactions to stimulants were observed when groups of 40 rats of each sex were fed (−)-or (±)-menthol in the diet for 5.5 weeks at doses of 0, 100, or 200 mg/kg bw per day." Based on these observations, the OECD SIDS dossier authors concluded that a NOAEL of 200 mg/kg/day could be determined since no effects on the liver were observed during a longer duration dietary study on *l*-menthol (Thorup et al., 1983). In another study, *d,l*-menthol (CAS # 1490-04-6) was administered via diet to groups of 10 B6C3F1 mice/sex/dose at concentrations of 0, 930, 1870, 7500, and 15000 ppm. The study was conducted to determine the dietary concentrations for a following 2-year carcinogenicity study. Mortality was reported among the treated animals; however, this was not due to test material administration. There was a decrease in bodyweight gain among the high-dose females as compared to the controls. There were reports of increases in the incidences of perivascular lymphoid hyperplasia and interstitial nephritis among the female mice in the 2 high-dose groups. Thus, the 2 concentrations selected for the chronic 2-year study were 2000 and 4000 ppm. A subsequent 2-year carcinogenicity study was conducted on *d,l*-menthol in 2% corn oil administered via diet to B6C3F1 mice (50/sex/dose) at concentrations of 0, 2000, or 4000 ppm for 103 weeks followed by a 1-week treatment-free period. There was a significant decrease in the survival among the high-dose females; however, there were no reports of test material-related tumors observed among the treated animals. Thus, under the conditions of this study, *d,l*-menthol was concluded to be non-carcinogenic for B6C3F1 mice. The NOAEL in mice was considered to be 2000 ppm (equivalent to 300 mg/kg/day, as per the conversion factors for mice, available in the JECFA guidelines for the preparation of toxicological working papers on food additives), based on decreased survival among the high-dose females (NCI, 1979). In another study, groups of 10 Fischer 344 rats/sex/dose were administered test material, *d,l*-menthol (CAS # 1490-04-6), via diet in 2% corn oil for 13 weeks at concentrations of 0, 930, 1870, 7500, and 15000 ppm. The study was conducted to determine the dietary concentrations for a subsequent 2-year carcinogenicity study. There were incidences of interstitial nephritis reported among the high-dose males. There were no other treatment-related alterations reported during the 13-week treatment. Based on these results, the concentrations for the chronic 2-year study were determined to be 3700 and 7500 ppm *d,l*-Menthol in 2% corn oil was administered via diet to Fischer 344 rats (50/sex/dose) at concentrations of 3700 and 7500 ppm. There were no significant differences in survival rates among the treated animals. Based on the histopathologic examination, *d,l*-menthol was neither toxic nor carcinogenic to Fischer 344 rats under the conditions of this study. Thus, the NOAEL was considered to be 7500 ppm or 750 mg/kg/day (using conversion factors for rats, available in the JECFA guidelines for the preparation of toxicological working papers on food additives), the highest dose tested (NCI, 1979). The most conservative NOAEL of 300 mg/kg/day from the long-term 2-year carcinogenicity study in mice was considered for the repeated dose toxicity endpoint. **Therefore, the cyclohexanol,4-(3-methylbutyl)- MOE can be calculated by dividing the *d,l*-menthol NOAEL in mg/kg/day by the total systemic exposure to cyclohexanol,4-(3-methylbutyl)-, 300/0.011 or 27273.**

The RIFM Criteria Document (Api et al., 2015) calls for a default margin of exposure of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for cyclohexanol, 4-(3-methylbutyl)- was calculated by dividing the NOAEL of 300 mg/kg/day by the uncertainty factor 100 = 3.00 mg/kg/day.

In addition, the total systemic exposure to cyclohexanol,4-(3-methylbutyl)- (11 μg/kg/day) is below the TTC (30 μg/kg bw/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: 05/12/18.

10.1.3. Reproductive toxicity

The margin of exposure for cyclohexanol,4-(3-methylbutyl)- is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient fertility data on cyclohexanol,4-(3-methylbutyl)- or on any read-across materials. The total systemic exposure to cyclohexanol, 4-(3-methylbutyl)- is below the TTC for the fertility endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are insufficient developmental toxicity data on cyclohexanol,4-(3-methylbutyl)-. Read-across materials menthol (CAS # 89-78-1; see Section V) and *d,l*-menthol (isomer unspecified; CAS # 1490-04-6; see Section V) have sufficient developmental toxicity data. Menthol has gavage developmental toxicity studies conducted in mice, rats, hamsters, and rabbits. Groups of 22–23 pregnant albino CD-1 mice/dose group were administered menthol in corn oil via gavage at doses of 0, 1.85, 8.59, 39.9, and 185 mg/kg/day from day 6 through day 15 of gestation. There were no effects on implantation or maternal and fetal survival among treated animals as compared to the control group up to the highest dose tested (FDA, 1973). The NOEL for maternal and developmental toxicity was considered to be 185 mg/kg/day. In another study, groups of 22–25 pregnant Wistar rats/dose group were administered menthol in corn oil via gavage at doses of 0, 2.18, 10.15, 47.05, and 218 mg/kg/day from day 6 through day 15 of gestation. Menthol produced no effects among the treated animals when compared to the control group up to the highest dose tested. The NOEL for maternal and developmental toxicity was considered to be 218 mg/kg/day (FDA, 1973). In another study, groups of 21–23 pregnant Syrian hamsters/dose group were administered menthol in corn oil via gavage at doses of 0, 4.05,

21.15, 98.2, and 405 mg/kg/day from day 6 through day 10 of gestation. Menthol produced no effects among the treated animals when compared to the control group up to the highest dose tested. The NOEL for maternal and developmental toxicity was considered to be 405 mg/kg/day (FDA, 1973). In another study, groups of 11–14 pregnant rabbits/dose group were administered menthol in corn oil via gavage at doses of 0, 4.25, 19.75, 91.7, and 425 mg/kg/day from day 6 through day 18 of gestation. Mortality was reported among the treated and control animals. However, there was no dose responses and no alterations in clinical signs reported; hence, this finding was not considered to be treatment-related. In addition, no effect on maternal and fetal survival and no dose-related increases in the number of abnormalities in soft or skeletal tissues were observed up to the highest dose tested. Thus, the NOAEL for maternal and developmental toxicity was considered to be 425 mg/kg/day, the highest dosage tested (FDA, 1973). The NOAEL for developmental toxicity was determined to be 425 mg/kg/day, the highest dosage tested among the treated rabbits (FDA, 1973). **Therefore, the cyclohexanol,4-(3-methylbutyl)- MOE for the developmental toxicity endpoint can be calculated by dividing the menthol NOAEL in mg/kg/day divided by the total systemic exposure to cyclohexanol,4-(3-methylbutyl)-, 425/0.011 or 38636.**

In addition, the total systemic exposure to cyclohexanol,4-(3-methylbutyl)- (11 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on cyclohexanol,4-(3-methylbutyl)- or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to cyclohexanol, 4-(3-methylbutyl)- (11 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/06/2018.

10.1.4. Skin sensitization

Based on the existing data and read-across material 4-isopropylcyclohexanol (CAS # 4621-04-9), cyclohexanol, 4-(3-methylbutyl)- does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for cyclohexanol,4-(3-methylbutyl)-. Existing data and read-across material 4-isopropylcyclohexanol (CAS # 4621-04-9; see Section V) do not indicate cyclohexanol, 4-(3-methylbutyl)- is a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v4.1). A mixture of the cis (33.68%) and trans (65.87%) isomers of read-across material 4-isopropylcyclohexanol was found to be negative in an *in chemico* direct peptide reactivity assay (DPRA) and in an *in vitro* KeratinoSens (RIFM, 2015a; RIFM, 2015b). In a guinea pig maximization test with cyclohexanol, 4-(3-methylbutyl)-, no reactions indicative of sensitization were observed at 100% (RIFM, 2004). In a human maximization test, no skin sensitization reactions were observed at 5% of read-across material 4-isopropylcyclohexanol (RIFM, 1975). Additionally, in confirmatory HRIPTs, read-across material 4-isopropylcyclohexanol did not present reactions indicative of sensitization when tested at 5% (2500 µg/cm^2) in alcohol SD 39C, 1% (550 µg/cm^2) in 1:3 ethanol:diethyl phthalate (1:3 EtOH:DEP), and at 2% in dimethyl phthalate in 49, 106, and 50 volunteers, respectively (RIFM, 1983; RIFM, 2012; RIFM, 1960).

Based on existing data and read-across material 4-isopropylcyclohexanol, cyclohexanol,4-(3-methylbutyl)- does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/06/2018.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, cyclohexanol,4-(3-methylbutyl)- would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for cyclohexanol,4-(3-methylbutyl)- in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, cyclohexanol, 4-(3-methylbutyl)- does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/11/18.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for cyclohexanol,4-(3-methylbutyl)- is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on cyclohexanol,4-(3-methylbutyl)-. Based on the Creme RIFM Model, the inhalation exposure is 0.066 mg/day. This exposure is 21.2 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/24/2018.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of cyclohexanol,4-(3-methylbutyl)- 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, cyclohexanol, 4-(3-methylbutyl)- 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 cyclohexanol, 4-(3-methylbutyl)- possibly 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.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), cyclohexanol, 4-(3-methylbutyl)- presents no risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2007d: The ready biodegradability of the test material was determined by the Manometric Respirometric Test according to the OECD 301F method. Under the conditions of the study, no biodegradation was observed after 28 days.

10.2.2.2. Ecotoxicity. RIFM, 2007c: An acute *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 of the test material was reported to be 7.86 mg/L.

10.2.2.3. Other available data. Cyclohexanol,4-(3-methylbutyl)-has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

Since cyclohexanol,4-(3-methylbutyl)- has passed the screening criteria, measured data was included for completeness only and has not been used in PNEC derivation.

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>4.612</u>			1,000,000	0.004612	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.95	3.95
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 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 0.004612 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the currently reported volumes of use.

Literature Search and Risk Assessment Completed On: 5/2/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 08/27/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2018.11.051.

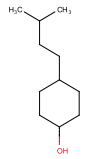
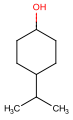
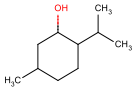
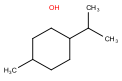
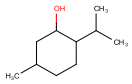
Appendix

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, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- 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), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Materials			
Principal Name	Cyclohexanol,4-(3-methyl-butyl)-	4-Isopropylcyclohexanol	*l*-Menthol	Menthol	*d,l*-Menthol (isomer unspecified)
CAS No.	830322-14-0	4621-04-9	2216-51-5	89-78-1	1490-04-6
Structure					
Similarity (Tanimoto Score)		0.66	0.65	0.65	0.65
Read-across Endpoint		• Skin Sensitization	• Repeated dose toxicity	• Developmental toxicity	• Developmental toxicity • Repeated Dose Toxicity
Molecular Formula	$C_{11}H_{22}O$	$C_9H_{18}O$	$C_{10}H_{20}O$	$C_{10}H_{20}O$	$C_{10}H_{20}O$
Molecular Weight	170.30	142.24	156.27	156.27	156.27
Melting Point (°C, EPI Suite)	8.80	−13.43	−5.90	−5.90	−5.90
Boiling Point (°C, EPI Suite)	242.74	205.20	218.94	218.94	218.94
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.692	7.18	1.02	1.02	1.02
Log Kow (KOWWIN v1.68 in EPI Suite)	3.95	2.96	3.19	3.19	3.19
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	84.67	780.9	490	490	490
J_{max} (mg/cm^2/h, SAM)	40.285	140.352	45.301	45.301	45.301
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	2.05E+000	1.16E+000	1.54E+000	1.54E+000	1.54E+000
Repeated dose (HESS)	• Not categorized		• Not categorized		• Not categorized
ER Binding (OECD QSAR Toolbox v4.2)	• Moderate binder, OH grooup			• Weak binder, OH group	• Weak binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good reliability)			• Toxicant (good reliability)	• Toxicant (good reliability)
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			
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	See Supplemental Data 5

Summary

There are insufficient toxicity data on cyclohexanol,4-(3-methylbutyl)- (CAS # 830322-14-0). 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, 4-Isopropylcyclohexanol (CAS # 4621-04-9), *l*-menthol (CAS # 2216-51-5), menthol (CAS # 89-78-1), and *d,l*-menthol (isomer unspecified) (CAS # 1490-04-6) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 4-Isopropylcyclohexanol (CAS # 4621-04-9) was used as a read-across analog for the target material cyclohexanol, 4-(3-methylbutyl)- (CAS # 830322-14-0) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to a class of saturated cyclic secondary alcohols (cyclohexanols).
  - The target substance and the read-across analog share a cyclohexanol substructure.
  - The key difference between the target substance and the read-across analog is that the target substance has a 4-(3-methylbutyl) substituent, whereas the read-across analog has a 4-isopropyl substituent in the same position. This structural difference is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - There are no skin sensitization alerts for the target or the read-across analog. Data are consistent with *in silico* alerts.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- *l*-Menthol (CAS # 2216-51-5), menthol (CAS # 89-78-1), and *d,l*-menthol (isomer unspecified) (CAS # 1490-04-6) were used as a read-across analogs for the target material cyclohexanol, 4-(3-methylbutyl)- (CAS # 830322-14-0) for the repeated dose and reproductive toxicity endpoints.
  - The target substance and the read-across analogs are structurally similar and belong to a class of saturated cyclic secondary alcohols (cyclohexanols).
  - The target substance and the read-across analogs share a cyclohexanol substructure.
  - The key difference between the target substance and the read-across analogs is that the target substance has a 4-(3-methylbutyl) substitution while the read-across analogs have 2-isopropyl and 5-methyl substitutions. This structural difference is toxicologically insignificant.
  - Similarity between the target substance and the read-across analogs are indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analogs.
  - The target substance and the read-across analogs are predicted to be weak ER binders by the OECD QSAR toolbox and developmental toxicants by the CAESAR model. The data described in the repeated dose and developmental toxicity sections confirm that the margin of exposure for the read-across analogs is adequate at the current level of usage. Therefore, the alerts are superseded by data.
  - The target substance and the read-across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analogs and the target material.

Explanation of Cramer Classification

Due to potential discrepancies between 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.

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and 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? (see Cramer et al., 1978 for a detailed explanation)? No.
Q17. Readily hydrolyzed to a common terpene? No.
Q19. Open chain? No.
Q23. Aromatic? No.
Q24. Monocarbocyclic with simple substituents? Y.
Q18. One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories)? No, Class I (Class Low).

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