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Short Review

RIFM fragrance ingredient safety assessment, cyclohexanol, 2-methoxy-4-propyl-, CAS Registry Number 23950-98-3



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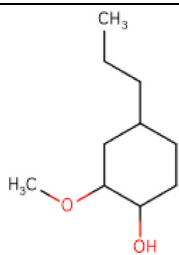
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Name: Cyclohexanol, 2-methoxy-4-propyl-
CAS Registry Number: 23950-98-3



Abbreviation/Definition List:

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

AF - Assessment Factor

BCF - Bioconcentration Factor

CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations

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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

EU - Europe/European Union

GLP - Good Laboratory Practice

HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals

IFRA - The International Fragrance Association

ISS - Istituto Superiore di Sanita (Italian National Institute of Health)

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

OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)

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

Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach

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

(continued)

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.

Cyclohexanol, 2-methoxy-4-propyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog menthol (CAS # 89-78-1) show that cyclohexanol, 2-methoxy-4-propyl- is not expected to be genotoxic. Data on read-across analog *trans*-4-tert-butylcyclohexanol (CAS # 21862-63-5) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and developmental toxicity endpoints. The fertility and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to cyclohexanol, 2-methoxy-4-propyl- is below the TTC (0.0015 mg/kg/day and 0.47 mg/day, respectively). Data from read-across analog *l*-menthol (CAS # 2216-51-5) show that there are no safety concerns for cyclohexanol, 2-methoxy-4-propyl- for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on the absence of a chromophore/UV active functional group; cyclohexanol, 2-methoxy-4-propyl- is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; cyclohexanol, 2-methoxy-4-propyl- 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 (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2018a; ECHA, 2011)

Repeated Dose Toxicity: NOAEL = 240 mg/kg/day. (RIFM (2011))

Reproductive Toxicity: Developmental toxicity: NOAEL = 600 mg/kg/day. Fertility: No NOAEL available. Exposure is below the TTC. (RIFM (2013))

Skin Sensitization: Not a concern for skin sensitization. (RIFM, 2018b; RIFM, 2018c; RIFM, 1995)

Photoirritation/Photoallergenicity: Not expected to be photoirritating or photoallergenic.

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.96 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 13 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 155.4 mg/L (RIFM Framework; Salvito, 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, 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 155.4 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.1554 µg/L

• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

(continued on next column)

1. Identification

- Chemical Name:** Cyclohexanol, 2-methoxy-4-propyl-
- CAS Registry Number:** 23950-98-3
- Synonyms:** 2-Methoxy-4-propylcyclohexanol; Tarragol; Cyclohexanol, 2-methoxy-4-propyl-
- Molecular Formula:** C₁₀H₂₀O₂
- Molecular Weight:** 172.26 g/mol
- RIFM Number:** 9420
- Stereochemistry:** No isomer specified. Three stereocenters are present, and 8 total stereoisomers are possible.

2. Physical data

- Boiling Point:** 248.97 °C (EPI Suite v4.11)
- Flash Point:** Not Available
- Log Kow:** 2.20 (EPI Suite v4.11)
- Melting Point:** 21.48 °C (EPI Suite v4.11)
- Water Solubility:** 2576 mg/L at 25 °C (EPI Suite v4.11)
- Specific Gravity:** Not Available
- Vapor Pressure:** 0.00348 mm Hg at 25 °C; 0.464 Pa at 25 °C (EPI Suite v4.11)
- UV Spectra:** Not available
- Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year	IFRA (2019)
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4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.5)

1. 95th Percentile Concentration in Fine Fragrance: 0.12%	RIFM (2021)
2. Inhalation Exposure*: 0.000017 mg/kg/day or 0.0012 mg/day	RIFM (2021)
3. Total Systemic Exposure**: 0.0012 mg/kg/day	RIFM (2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; 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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. Cramer Classification: Class III, High

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.6
III	III	III

2. Analogs Selected:

- Genotoxicity:** Menthol (CAS # 89-78-1); WoE to 3,7-dimethyl-7-methoxyoctan-2-ol (CAS # 41890-92-0)
- Repeated Dose Toxicity:** *trans*-4-*tert*-Butylcyclohexanol (CAS # 21862-63-5)
- Reproductive Toxicity:** *trans*-4-*tert*-Butylcyclohexanol (CAS # 21862-63-5)
- Skin Sensitization:** *l*-Menthol (CAS # 2216-51-5)
- Photoirritation/Photoallergenicity:** None
- Local Respiratory Toxicity:** None
- Environmental Toxicity:** None

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

Cyclohexanol, 2-methoxy-4-propyl- 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

Cyclohexanol, 2-methoxy-4-propyl- has been pre-registered for 2010; no dossier available as of 02/23/24.

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, cyclohexanol, 2-methoxy-4-propyl- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Cyclohexanol, 2-methoxy-4-propyl- was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (Etter et al., 2015). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays 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 cyclohexanol, 2-methoxy-4-propyl-; however, read-across can be made to menthol (CAS # 89-78-1; see Section VI).

The mutagenic activity of menthol 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA

were treated with menthol in dimethyl sulfoxide 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, 2018a). Under the conditions of the study, menthol was not mutagenic in the Ames test, and this can be extended to cyclohexanol, 2-methoxy-4-propyl-.

As an additional weight of evidence (WoE), the mutagenic activity of 3,7-dimethyl-7-methoxyoctan-2-ol (CAS # 41890-92-0) 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 method. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2016a). Under the conditions of the study, 3,7-dimethyl-7-methoxyoctan-2-ol was not mutagenic in the Ames test, and this can be extended to cyclohexanol, 2-methoxy-4-propyl-.

The clastogenicity of menthol was assessed in an *in vitro* chromosome aberration study. Chinese hamster ovary cells were treated with menthol at concentrations up to 5 mg/mL (5000 µg/mL) in the presence and absence of metabolic activation (solvent not specified). 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 (ECHA, 2011). Under the conditions of the study, menthol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to cyclohexanol, 2-methoxy-4-propyl-.

As an additional WoE, the clastogenic activity of 3,7-dimethyl-7-methoxyoctan-2-ol (CAS # 41890-92-0) was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. 3,7-Dimethyl-7-methoxyoctan-2-ol did not induce binucleated cells with micronuclei when tested up to the cytotoxic (50%–60% reduction in cytokinesis-blocked proliferation index (CBPI) or the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2016b). Under the conditions of the study, 3,7-dimethyl-7-methoxyoctan-2-ol was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to cyclohexanol, 2-methoxy-4-propyl-.

Based on the data available, menthol and 3,7-dimethyl-7-methoxyoctan-2-ol does not present a concern for genotoxic potential, and this can be extended to cyclohexanol, 2-methoxy-4-propyl-.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/05/23.

11.1.2. Repeated dose toxicity

The MOE for cyclohexanol, 2-methoxy-4-propyl- 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 on cyclohexanol, 2-methoxy-4-propyl-. Read-across material *trans*-4-tert-butylcyclohexanol (CAS# 21862-63-5; see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

In an OECD 408- and GLP-compliant study, 10 SPF-bred Wistar rats/sex/dose were administered *trans*-4-tert-butylcyclohexanol via gavage at doses of 80, 240, and 800 mg/kg/day. Two control groups of 10 SPF-bred Wistar rats/sex each were administered the vehicle (corn oil) and 10% ethanol, or only the vehicle. An additional 5 SPF-bred Wistar rats/sex/group were maintained in the 2 control groups and high-dose group for a 28-day recovery period after treatment. Mortality was seen in the ethanol control (1 male), at the mid dose (1 female), and at the high dose (1 female and 1 male). No treatment-related effects were reported in clinical signs, behavioral observations, functional observation battery, grip strength, locomotor activity, food consumption, and ophthalmology. Body weight and bodyweight gain were slightly reduced in females at the mid dose and were reduced in both sexes at the high dose.

Body weight was reversed during the recovery period, but bodyweight gain persisted through the recovery period at the high dose. Several hematological changes occurred in both sexes at the high dose but were all reversed during the recovery period. Many clinical chemistry changes occurred in both sexes at each dose level. Most clinical chemistry changes remained within historical controls, except for increased triglyceride levels in females at the high dose and increased phospholipid and globulin levels in males at the high dose. All clinical chemistry changes were reversed during the recovery period. Some urinary changes were reported but remained within historical control ranges and were reversed during the recovery period. Absolute and relative kidney weights were increased in males at all doses. Absolute liver weight was increased in males in the mid and high doses. Relative liver weight was increased in males at the mid dose and both sexes at the high dose. All organ weight changes were reversed during the recovery period except for increased relative kidney weights in males at the high dose. Accentuated lobular pattern was found in the liver in males at the mid dose (2/10) and the high dose (3/10). Kidney discoloration was seen in the males at the mid dose (1/10) and the high dose (2/10). Signs of α -2u-globulin nephropathy were found in males at all doses; however, this is sex- and species-specific and, thus, not relevant to human health. Tubular cysts were seen in both sexes at the high dose. Based on clinical chemistry changes observed at 800 mg/kg/day, the NOAEL for this study was concluded to be 240 mg/kg/day (RIFM, 2011).

Therefore, the cyclohexanol, 2-methoxy-4-propyl- MOE can be calculated by dividing the NOAEL for 4-*tert*-butylcyclohexanol by the total systemic exposure to cyclohexanol, 2-methoxy-4-propyl-, 240/0.0012, or 200000.

In addition, the total systemic to cyclohexanol, 2-methoxy-4-propyl- (1.2 µg/kg/day) is below the TTC (1.5 µg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/17/23.

11.1.3. Reproductive toxicity

The MOE for cyclohexanol, 2-methoxy-4-propyl- is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient fertility data on cyclohexanol, 2-methoxy-4-propyl- or any read-across materials. The total systemic exposure to cyclohexanol, 2-methoxy-4-propyl- is below the TTC for the fertility endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on cyclohexanol, 2-methoxy-4-propyl-. Read-across material *trans*-4-tert-butylcyclohexanol (CAS# 21862-63-5; see Section VI) has sufficient data to support the developmental toxicity endpoint.

In an OECD 414- and GLP-compliant prenatal developmental toxicity study, 24 female Sprague Dawley rats/group were administered dose levels of 150, 300, and 600 mg/kg/day in corn oil via oral gavage from gestation days (GDs) 6–15 for 6 h/day. No mortality was observed. Treatment-related clinical signs (hypoactivity) were observed in 21 out of 24 dams during different days of gestation at the 600 mg/kg dose. No gross lesions were observed in dams during necropsy in any of the doses tested. No treatment-related or toxicologically relevant effects were seen in fetuses with respect to external, visceral, and skeletal examinations. The NOAEL for maternal toxicity was considered to be 300 mg/kg/day, based on treatment-related clinical signs of hypoactivity and/or salivation at 600 mg/kg/day. The NOAEL for developmental toxicity was considered to be 600 mg/kg/day, based on the absence of treatment-related adverse effects on the development of pups up to the highest dose tested (RIFM, 2013).

Therefore, the cyclohexanol, 2-methoxy-4-propyl- MOE for the developmental toxicity endpoint can be calculated by dividing the *trans*-

4-*tert*-butylcyclohexanol NOAEL in mg/kg/day by the total systemic exposure to cyclohexanol, 2-methoxy-4-propyl-, 600/0.0012, or 42857.

There are no fertility data on cyclohexanol, 2-methoxy-4-propyl- or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to cyclohexanol, 2-methoxy-4-propyl- (1.2 µg/kg/day) is below the TTC (1.5 µg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/17/23.

11.1.4. Skin sensitization

Based on the existing data on the target material and read-across material, *l*-menthol, cyclohexanol, 2-methoxy-4-propyl-, presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for cyclohexanol, 2-methoxy-4-propyl-. Therefore, *l*-menthol (CAS #

2216-51-5; see Section VI) was used for the risk assessment of cyclohexanol, 2-methoxy-4-propyl-. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, cyclohexanol, 2-methoxy-4-propyl- is not considered a skin sensitizer. Cyclohexanol, 2-methoxy-4-propyl- and read-across material *l*-menthol are predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.6). Read-across material isomer menthol was found to be negative in an *in vitro* KeratinoSens and human cell line activation test (h-CLAT) (RIFM, 2018c; RIFM, 2018b). The results were evaluated following the OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021), and based on the 2 out of 3 Defined Approach, read-across material isomer menthol is a non-sensitizer. A guinea pig Buehler test with cyclohexanol, 2-methoxy-4-propyl- did not present reactions indicative of sensitization (RIFM, 1989). In a murine local lymph node assay (LLNA), read-across material *l*-menthol was found to be non-sensitizing when tested up to 30% (7500 µg/cm²) (RIFM, 1995; ECHA, 2011). A guinea pig Buehler test with *l*-menthol did not present reactions indicative of sensitization (RIFM, 1990; ECHA, 2011). In a human

Table 1

Summary of existing data on *l*-menthol as a read-across for cyclohexanol, 2-methoxy-4-propyl-.

WoE Skin Sensitization Potency Category ¹	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm ²	NOEL-HMT (induction) µg/cm ²	LOEL (induction) µg/cm ²	WoE NESIL µg/cm ²	LLNA ² Weighted Mean EC3 Value µg/cm ²	GPMT	Buehler ³
No evidence of sensitization ⁵	N/A	5520	N/A	N/A	Negative up to 7500 (30%)	N/A	Negative
	<i>In vitro</i> Data ⁴				<i>In silico</i> protein binding alerts (OECD Toolbox v4.6)		
	KE 1	KE 2	KE 3	Target Material	Autoxidati on simulator	Metabolis m simulator	
N/A	Negative	Negative	No alert found	Radical reactions	Nucleophilic addition		

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; GPMT = Guinea Pig Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available.

¹WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

²Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

³Studies conducted according to the OECD TG 406 are included in the table.

⁴Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

⁵Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

maximization test, no skin sensitization reactions were observed with read-across material *I*-menthol (RIFM, 1974a). In a human maximization test, no skin sensitization reactions were observed with read-across material isomer menthol racemic (RIFM, 1973).

Based on the WoE from structural analysis, *in vitro*, animal, and human studies on the read-across material as well as the target material, cyclohexanol, 2-methoxy-4-propyl- does not present a concern for skin sensitization.

Additional References: Valosen (1999); Ishihara (1986); Xu (2006); Friedrich (2007); Sharp (1978); RIFM, 1974b.

Literature Search and Risk Assessment Completed On: 07/01/23.

11.1.5. Photoirritation/photoallergenicity

Based on the structural analysis, cyclohexanol, 2-methoxy-4-propyl- would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photosafety studies available for cyclohexanol, 2-methoxy-4-propyl- in experimental models. UV/Vis absorption spectra are not available. Structural analysis of cyclohexanol, 2-methoxy-4-propyl- revealed that a chromophore is not present. Without a chromophore present, absorbance of UV/Vis light is not possible. Based on the lack of a chromophore, cyclohexanol, 2-methoxy-4-propyl- does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were not available for cyclohexanol, 2-methoxy-4-propyl-. Structural analysis of the material revealed that a chromophore is not present. Without a chromophore, absorbance of UV/Vis light is not possible.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/04/24.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for cyclohexanol, 2-methoxy-4-propyl- 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 cyclohexanol, 2-methoxy-4-propyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.0012 mg/day. This exposure is 391.7 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: 07/01/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cyclohexanol, 2-methoxy-4-propyl- was performed following the RIFM Environmental Framework (Salvito, 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 of 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 VoU 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, 2-methoxy-4-propyl- 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, 2-methoxy-4-propyl- 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, 2017a). 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).

11.2.1.1. Risk assessment. Based on the current VoU (2019), cyclohexanol, 2-methoxy-4-propyl- presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Cyclohexanol, 2-methoxy-4-propyl- has been pre-registered for REACH with no additional data at this time.

11.2.1.3. Risk assessment refinement. Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} , Used	2.2	2.2
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU 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 0.1554 $\mu\text{g/L}$. 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: 07/21/23.

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/>

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>155.4</u>	X	X	1000000	0.1554	X

- **OECD Toolbox:** <https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm>
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubChem:** <https://pubchem.ncbi.nlm.nih.gov/>
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** <https://chemview.epa.gov/chemview/>
- **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://pubchem.ncbi.nlm.nih.gov/source/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 02/23/24.

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.2024.114566>.

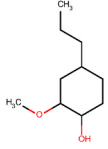
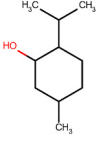
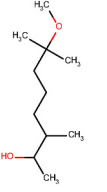
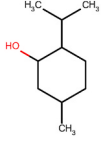
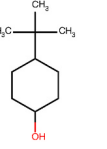
Appendix

Read-across Justification

Methods

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

- 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 (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 v4.6 (OECD, 2023).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.6 (OECD, 2023).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.6 (OECD, 2023).
- The major metabolites for the target material and read-across analogs were determined and evaluated using the OECD QSAR Toolbox v4.6 (OECD, 2023).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.6 was selected as the alert system.

Principal Name	Target Material	Read-across Material	Weight of Evidence Material	Read-across Material	Read-across Material
	Cyclohexanol, 2-methoxy-4-propyl-	Menthol	3,7-Dimethyl-7-methoxyoctan-2-ol	<i>l</i> -Menthol	<i>trans</i> -4-tert-Butylcyclohexanol
CAS No.	23950-98-3	89-78-1	41890-92-0	2216-51-5	21862-63-5
Structure					
Similarity (Tanimoto Score)		0.67	0.78	0.67	0.66
SMILES	CCCC1CCC(O)C(C1)OC	CC(C)C1CCC(C)CC1O	COC(C)(C)CCCC(C)C(C)O	CC(C)C1CCC(C)CC1O	CC(C)(C)C1CCC(O)CC1
Endpoint		Genotoxicity	Genotoxicity	Skin sensitization	Repeated dose toxicity Developmental toxicity
Molecular Formula	C ₁₀ H ₂₀ O ₂	C ₁₀ H ₂₀ O	C ₁₁ H ₂₄ O ₂	C ₁₀ H ₂₀ O	C ₁₀ H ₂₀ O
Molecular Weight (g/mol)	172.268	156.269	188.311	156.269	156.269
Melting Point (°C, EPI Suite)	21.48	79.50	8.24	79.50	62.00
Boiling Point (°C, EPI Suite)	248.97	216.00	229.67	216.00	216.91
Vapor Pressure (Pa @ 25° C, EPI Suite)	4.64E-01	8.49E+00	1.59E+00	8.49E+00	1.44E+00
Water Solubility (mg/L, @ 25° C, WSKOW v1.42 in EPI Suite)	2.58E+03	4.90E+02	7.07E+02	4.90E+02	1.00E+02
Log K_{OW}	2.2	3.19	2.76	3.19	3.09
J_{max} (µg/cm²/h, SAM)	44.88	45.30	19.81	45.30	8.36
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	1.36E-02	1.54E+00	4.09E-02	1.54E+00	1.54E+00
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.6)	No alert found	No alert found	No alert found		
DNA Binding (OECD QSAR Toolbox v4.6)	No alert found	No alert found	No alert found		
Carcinogenicity (ISS)	No alert found	No alert found	Structural alert for nongenotoxic carcinogenicity Substituted n-alkylcarboxylic acids (Nongenotox)		
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found		
In Vitro Mutagenicity (Ames, ISS)	No alert found	No alert found	No alert found		
In Vivo Mutagenicity (Micronucleus, ISS)	H-acceptor-path3-H-acceptor	No alert found	No alert found		
Oncologic Classification	Not classified	Not classified	Not classified		
Repeated Dose Toxicity					
Repeated Dose (HESS)	Not categorized				Not categorized
Developmental and Fertility Toxicity					
ER Binding (OECD QSAR Toolbox v4.6)	Moderate binder, OH group				Weak binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	NON-Toxicant (low reliability)				Toxicant (good reliability)
Skin Sensitization					
Protein Binding (OASIS v1.1)	No alert found			No alert found	
Protein Binding (OECD)	No alert found			No alert found	
Protein Binding Potency	Not possible to classify according to these rules (GSH)			Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found			No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.			No skin sensitization reactivity domains alerts identified.	
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.6)	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, 2-methoxy-4-propyl- (CAS # 23950-98-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical-chemical properties, and expert judgment, menthol

(CAS # 89-78-1), *l*-menthol (CAS # 2216-51-5), and *trans*-4-*tert*-butylcyclohexanol (CAS # 21862-63-5) were identified as read-across analogs, and 3,7-dimethyl-7-methoxyoctan-2-ol (CAS # 41890-92-0) was identified as a WoE material with sufficient data for toxicological evaluation.

Conclusions

- Menthol (CAS # 89-78-1) was used as a read-across analog for the target material, cyclohexanol, 2-methoxy-4-propyl- (CAS # 23950-98-3), for the genotoxicity endpoint.
 - o The target material and the read-across analog are both mono cyclic secondary alcohols with alkyl substitution.
 - o The key difference between the target material and the read-across analog is that the read-across analog does not contain the ether functionality found in the target material. Therefore, to satisfy the structural domain of the target material, substance Menthol (CAS # 41890-92-0) is used as WoE. This chemical contains both the secondary alcohol and ether functionality similar to the target material. The read-across analog, combined with the WoE material, 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 v4.6, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
 - o The target material contains an *in silico* alert for H-acceptor-path3-H-acceptor while the read-across analog does not (genotoxicity). The data from the genotoxicity section confirms that the read-across analog is not genotoxic. Therefore, based on the structural similarity between the target material and the read-across analog and the data for the read-across analog, predictions are superseded by data.
 - o The weight of evidence material has an *in silico* alert for nongenotoxic carcinogenicity|substituted n-alkylcarboxylic acids (nongenotox). According to these predictions, the weight of evidence material is expected to be more reactive compared to the target material. Data superseded predictions in this case.
 - 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, cyclohexanol, 2-methoxy-4-propyl- (CAS # 23950-98-3), for the skin sensitization endpoint.
 - o The target material and the read-across analog are both cyclohexanols.
 - o The key difference between the target material and the read-across analog is that the target material has an additional ether functionality. This structural difference is toxicologically insignificant.
 - 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 v4.6, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
 - o Neither the read-across analog nor the target material display *in silico* alerts for the skin sensitization endpoint. The data from the skin sensitization section confirms the material presents no concern. *In silico* alerts are 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.
- *trans*-4-*tert*-Butylcyclohexanol (CAS # 21862-63-5) was used as a read-across analog for the target material, cyclohexanol, 2-methoxy-4-propyl- (CAS # 23950-98-3), for the repeated dose toxicity and developmental toxicity endpoints.
 - o The target material and the read-across analog are both cyclohexanols.
 - o The key difference between the target material and the read-across analog is that the target material has an additional ether functionality. This structural difference is toxicologically insignificant.
 - 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 Differences are predicted for J_{\max} , which estimates skin absorption. J_{\max} for the target material corresponds to skin absorption $\leq 80\%$, and J_{\max} for the read-across analog corresponds to skin absorption $\leq 40\%$. While the percentage of skin absorption estimated from J_{\max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
 - o According to the OECD QSAR Toolbox v4.6, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
 - o The read-across analog has an *in silico* alert for Toxicant (Developmental toxicity). According to these predictions, the read-across analog is expected to be more reactive compared to the target material. Data superseded predictions in this case.
 - 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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