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Short Review

2nd update to RIFM fragrance ingredient safety assessment, 4-carvomenthenol, CAS Registry Number 562-74-3

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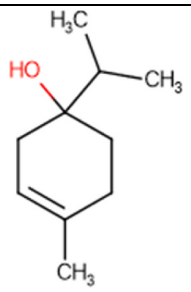


Name: 4-Carvomenthenol
CAS Registry Number: 562-74-3
Additional CAS Numbers*:
2438-10-0 (−)-Terpinen-4-ol
20126-76-5 (+)-Terpinen-4-ol
*Included because the materials are isomers

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, 2017; Safford et al., 2015, 2017, 2024) 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
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (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

(*continued on next column*)

(*continued*)

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.

4-Carvomenthenol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 4-carvomenthenol is not genotoxic. Data on read-across analog terpineol (CAS # 8000-41-7) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints. Data from read-analog α-bisabolol (CAS # 515-69-5) provided a No Expected Sensitization Induction Level (NESIL) of 5500 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 4-carvomenthenol is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; 4-carvomenthenol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients (RQs), 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 genotoxic.	(RIFM, 2000b; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 578 mg/kg/day.	ECHA (2017a)
Reproductive Toxicity: Developmental toxicity NOAEL = 200 mg/kg/day. Fertility NOAEL = 250 mg/kg/day.	(ECHA, 2010; ECHA, 2013)
Skin Sensitization: NESIL = 5500 μg/cm^2.	(RIFM, 2010b; Anderson et al., 2009)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 20 mg/m^3.	ECHA (2017a)

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Critical Measured Value: 95 % (OECD 301B)	ECHA (2023)
Bioaccumulation:	
Screening-level: 65.76 L/kg	US EPA (2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 5.18 mg/L	US EPA (2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 5.18 mg/L	US EPA (2012b)

RIFM PNEC is: 0.518 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** 4-Carvomenthenol 2. **CAS Registry Number:** 562-74-3 3. **Synonyms:** 3-Cyclohexen-1-ol, 4-methyl-1-(1-methylethyl)-; 1-*p*-Menthen-4-ol; 1-Methyl-4-isopropyl-1-cyclohexene-4-ol; Origanol; 4-Terpinenol; ｼﾞｱﾙｷﾙ(C = 1–3)ｼｸﾛﾍｷｾﾉｰﾙ; ﾃﾙﾋﾞﾈﾝ-4-ｵｰﾙ; 1-Isopropyl-4-methylcyclohex-3-en-1-ol; Terpinenol-4 NAT; Terpinenol-4 Pure; Terpineol-4; Terpinene-4-ol; Terpinen-4-ol; Terpin-4-ol; 4-Carvomenthenol 4. **Molecular Formula:** $C_{10}H_{18}O$ 5. **Molecular Weight:** 154.25 g/mol 6. **RIFM Number:** 932 7. **Stereochemistry:** Isomer not specified. One stereocenter is present, and 2 total stereoisomers are possible.	1. **Chemical Name:** (+)-Terpinen-4-ol 2. **CAS Registry Number:** 2438-10-0 3. **Synonyms:** (1S)-4-Methyl-1-(1-methylethyl)-3-cyclohexen-1-ol; (4S)-Terpinen-4-ol; (+)-Terpinen-4-ol 4. **Molecular Formula:** $C_{10}H_{18}O$ 5. **Molecular Weight:** 154.25 g/mol 6. **RIFM Number:** N/A 7. **Stereochemistry:** S isomer specified. One stereocenter is present, and 2 total stereoisomers are possible.	**Chemical Name:** (−)-Terpinen-4-ol **CAS Registry Number:** 20126-76-5 **Synonyms:** (1R)-4-Methyl-1-(1-methylethyl)-3-cyclohexen-1-ol; (R)-4-Carvomenthenol; L-4-Terpineol; (−)-Terpinen-4-ol **Molecular Formula:** $C_{10}H_{18}O$ **Molecular Weight:** 154.25 g/mol **RIFM Number:** N/A **Stereochemistry:** R isomer specified. One stereocenter is present, and 2 total stereoisomers are possible.

2. Physical data*

1. **Boiling Point:** 89 °C at 6 mm Hg (Fragrance Materials Association [FMA]), 214–219 °C (corrected to normal atmospheric pressure of 1013 hPa) (RIFM, 2016b), 211.85 °C (EPI Suite v4.11)
2. **Flash Point:** 82 °C (Globally Harmonized System), 179 °F; closed cup (FMA), 84.0 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2016a)
3. **Log K_{OW}:** 3.33 (EPI Suite v4.11)
4. **Melting Point**: 21 to −23 °C (at atmospheric pressure of 991 hPa or 1012 hPa, respectively) (RIFM, 2016b), 14.86 °C (EPI Suite v4.11)
5. **Water Solubility:** 386.6 mg/L at 25 °C (EPI Suite v4.11), 848 mg/L at 20 °C ± 2 °C (RIFM, 2000c), 2.81 g/L at 20 °C (pH 6.6) (RIFM, 2016d)
6. **Specific Gravity:** 0.936 (FMA)
7. **Vapor Pressure:** 0.02 mm Hg at 20 °C (FMA), 0.0427 mm Hg (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid that is very slightly soluble in water and soluble in alcohol, propylene glycol, and oils. Warm-peppery, mildly earthy, musty, woody odor of moderate tenacity. The taste is rather bitter at concentrations higher than 100 ppm, while it becomes quite pleasant, warm herbaceous peppery below 50 ppm (Arctander, 1969).

**In silico* (EPI Suite v4.11) physical data are identical for all materials.

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.4.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.011 % (RIFM, 2023)
2. **Inhalation Exposure*:** 0.000030 mg/kg/day or 0.0022 mg/day (RIFM, 2023)
3. **Total Systemic Exposure**:** 0.00046 mg/kg/day (RIFM, 2023)

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

**95th percentile calculated exposure; assumes 100 % absorption unless modified by dermal absorption data as reported in Section 5. 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, 2017; Safford et al., 2015, 2017, 2024).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.6 (OECD, 2023)
I	III	I

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Terpineol (CAS # 8000-41-7)
   c. **Reproductive Toxicity:** Terpineol (CAS # 8000-41-7)
   d. **Skin Sensitization:** α-Bisabolol (CAS # 515-69-5)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Terpineol (CAS # 8000-41-7)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

8. Natural occurrence

4-Carvomenthenol is reported to occur in the following foods by the VCF*.

Anise brandy	Beer (non-categorized)
Caraway (*Carum carvi* L.)	Pepper (*Piper nigrum* L.)
Dill (*Anethum* species)	Raspberry brandy
Grape (*Vitis* species)	Tequila (*Agave tequilana*)
Mammee apple (*Mammea americana* L.)	Wine

(+)-Terpinen-4-ol is reported to occur in the following foods by the VCF:

Citrus fruits.

Mastic (*Pistacia lentiscus*)
Tea.
Wild marjoram (*Origanum vulgare* L. ssp. hirtum)

(−)-Terpinen-4-ol is reported to occur in the following foods by the VCF:

Citrus fruits.
Mastic (*Pistacia lentiscus*)
Tea.
Wild marjoram (*Origanum vulgare* L. ssp. virens and vulgare)

*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. This is a partial list.

9. Reach dossier

Available for 4-carvomenthenol (ECHA, 2023) and (−)-terpinen-4-ol (ECHA, 2017d); accessed on 04/03/25; no dossier available for (+)-terpinen-4-ol as of 04/03/25.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 4-carvomenthenol 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)	0.42
2	Products applied to the axillae	0.13
3	Products applied to the face/body using fingertips	2.5
4	Products related to fine fragrances	2.4
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.60
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.60
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.60
5D	Baby cream, oil, talc	0.20
6	Products with oral and lip exposure	1.4
7	Products applied to the hair with some hand contact	4.8
8	Products with significant ano-genital exposure (tampon)	0.20
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.6
10A	Household care products with mostly hand contact (hand dishwashing detergent)	2.9
10B	Aerosol air freshener	17
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.20
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 linolenic acid, the basis was a reference dose of 2.0 mg/kg/day, a predicted skin absorption value of 80 %, and a skin sensitization NESIL of 5500 μg/cm^2.
As a conservative approach, we assumed that 100 % of the material exposed via the skin is bioavailable (see Section 5), thereby deriving the most stringent MOE. Since the MOE is > 100 (see the repeated dose and reproductive toxicity sections), we then refined the exposure to 80 % using an *in silico* Skin Absorption Model (SAM) to determine the Maximum Allowable Concentrations for each category listed in Section 10.
[b]For a description of the categories, refer to the IFRA/RIFM Information Booklet (https://ifrafragrance.org/docs/default-source/51st-amendment/ifra-51st-amendment—guidance-for-the-use-of-ifra-standards.pdf?sfvrsn = 79750005_2; June 2023).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.4.6.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 4-carvomenthenol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 4-Carvomenthenol was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80 % relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 4-carvomenthenol 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. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA97a, and TA102 were treated with 4-carvomenthenol in dimethyl sulfoxide (DMSO) at concentrations up to 5 mg/plate (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, 2000b). Under the conditions of the study, 4-carvomenthenol was not mutagenic in the Ames test.

The clastogenic activity of 4-carvomenthenol was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 4-carvomenthenol in DMSO at concentrations up to 1540 μg/mL in the dose range finding study; in the main study, micronuclei analysis was conducted at concentrations up to 1540 μg/mL in the presence and absence of metabolic activation. 4-Carvomenthenol did induce statistically significant increases in binucleated cells with micronuclei when tested up to cytotoxic concentrations at 400 μg/mL in the 4-h treatment with S9 (RIFM, 2015). However, the increase was within the historical control range and negative for dose response, so the result was considered not biologically relevant. Under the conditions of the study, 4-carvomenthenol was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 4-carvomenthenol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/23/24.

11.1.2. Repeated dose toxicity

The MOE for 4-carvomenthenol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. The repeated dose toxicity data on 4-carvomenthenol are insufficient for the repeated dose toxicity endpoint. Read-across material terpineol (CAS # 8000-41-7; see Section 6) has sufficient repeated dose toxicity data.

In a GLP/OECD 413 guideline study, Crl:CD(SD) male and female rats (10/sex/group) were exposed to terpineol multiconstituent by snout-only inhalation route at 0.202, 0.572, and 2.23 mg/L (actual

levels) for 13 weeks (6 h/day; 5 days/week), corresponding to 0, 52, 148 or 578 mg/kg/day according to standard minute volume and body weight parameters for Sprague Dawley rats. The mass median aerodynamic diameter (MMAD) was between 0.52 and 1.6 μM, and the respective geometric standard deviation (GSD) was between 2.99 and 1.75. A 4-week, treatment-free recovery group of 10/sex/group of control and high-dose group animals was also included. The nasal cavity was identified as a target organ for local effects. A significant reduction in mean group bodyweight gain among males of the high-dose group was observed. Examination of recovery phase animals showed no changes in the nasal pharynx respiratory epithelium, suggesting complete recovery after 4 weeks, which is therefore not considered adverse. The group mean reticulocyte percentage and the absolute reticulocyte count were significantly lower than control values for males of the high-dose group. This alteration was not present among the recovery group animals. In addition, there were no other related hematological alterations reported among treatment or recovery group animals as compared to the control. Thus, the NOAEL for the repeated dose toxicity endpoint was determined to be 2.23 mg/L, the highest dose tested, equivalent to 578 mg/kg/day according to standard minute volume and body weight parameters for Sprague Dawley rats (ECHA, 2017a; the ECHA dossier on this material uses terpineol data as read-across).

In another study, an OECD 422 gavage combined repeated dose toxicity study with the reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. There were 3 treatment groups. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at top dose: 5 males/dose) administered terpineol at doses of 0, 60, 250, and 750 mg/kg/day. The toxicity subgroup consisted of 5 females/dose group and 10 males/dose group, administered terpineol at doses of 0, 60, 250, and 750 mg/kg/day. Main-phase males and toxicity-phase females were dosed daily for a minimum of 5 consecutive weeks. An additional 5 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for 5 weeks and then given 2 weeks of recovery before termination. Although there were alterations in liver weight, clinical chemistry, and histopathological alterations, all the effects were reversible and hence not considered adaptive and not adverse (Hall et al., 2012). Histopathological changes associated with hyaline droplets were observed in the kidneys of male rats receiving 250 or 750 mg/kg/day; such changes are commonly associated with the administration of volatile hydrocarbons and are of no consequence to human risk assessment (Lehman-McKeeman, 1992; Lehman-McKeeman et al., 1990). In addition, the kidney weights and histopathology among recovery group animals were similar to the control. The repeated dose toxicity NOAEL was determined to be 750 mg/kg/day, the highest dose tested (ECHA, 2013; the ECHA dossier on this material uses terpineol data as read-across).

The most conservative NOAEL of 578 mg/kg/day from the 90-day inhalation toxicity study was selected for the repeated dose toxicity endpoint.

Therefore, the 4-carvomenthenol MOE for the repeated dose toxicity endpoint can be calculated by dividing the terpineol NOAEL in mg/kg/day by the total systemic exposure to 4-carvomenthenol, 578/0.00046, or 1256522.

In addition, the total systemic exposure to 4-carvomenthenol (0.46 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/17/24.

11.1.3. Reproductive toxicity

The MOE for 4-carvomenthenol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 4-carvomenthenol. Read-across material terpineol (CAS # 8000-41-7) was used to support the reproductive toxicity endpoint.

An OECD 422 gavage combined repeated dose toxicity study with the reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. There were 3 treatment groups. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at top dose: 5 males/dose) administered terpineol at doses of 0, 60, 250, and 750 mg/kg/day. The toxicity subgroup consisted of 5 females/dose group and 10 males/dose group, administered terpineol at doses of 0, 60, 250, and 750 mg/kg/day. Main-phase males and toxicity-phase females were dosed daily for a minimum of 5 consecutive weeks. An additional 10 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for 5 weeks and then given 2 weeks of recovery before termination. There were no adverse effects on the development of the fetus up to 250 mg/kg/day. At 750 mg/kg/day, no females became pregnant. It is considered that the testicular and epididymal effects observed in males receiving 750 mg/kg/day would have been sufficient to prevent fertilization. Thus, the NOAEL for the developmental toxicity endpoint was determined to be more than 250 mg/kg/day (ECHA, 2013; the ECHA dossier on this material uses terpineol data as read-across).

In another study, terpineol multiconstituent diluted in corn oil was administered by gavage to groups of mated female Sprague Dawley rats (20 mated females/dose) at the dose levels of 0, 60, 200, 600 mg/kg bw/day from days 6–19 after mating. The test was conducted according to the OECD 414 protocol. Embryo-fetal growth was slightly reduced by maternal treatment, as evidenced by reduced mean male and female fetal weight at 600 mg/kg/day. In addition, the mean placental weight in this dose group was slightly low, with differences attaining statistical significance. Mean placental, litter, and fetal weights at 60 or 200 mg/kg/day were unaffected by maternal treatment with terpineol. The incidence of major and minor abnormalities and skeletal variants showed no relationship to maternal treatment with terpineol. Thus, the NOAEL for the developmental toxicity was determined to be 200 mg/kg/day (ECHA, 2010; the ECHA dossier on this material uses terpineol data as read-across).

The most conservative NOAEL of 200 mg/kg/day was selected for the developmental toxicity endpoint.

Therefore, the terpineol MOE for the developmental toxicity endpoint can be calculated by dividing the terpineol NOAEL by the total systemic exposure to 4-carvomenthenol, 200/0.00046 or 434783.

An OECD 422 gavage combined repeated dose toxicity study with the reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. There were 3 treatment groups. There were 3 treatment groups. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at top dose: 5 males/dose) administered terpineol at doses of 0, 60, 250, and 750 mg/kg/day. The toxicity subgroup consisted of 5 females/dose group and 10 males/dose group, administered terpineol at doses of 0, 60, 250, and 750 mg/kg/day. Main-phase males and toxicity-phase females were dosed daily for a minimum of 5 consecutive weeks. An additional 10 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for 5 weeks and then given 2 weeks of recovery before termination. Testis weight was markedly low in males receiving 750 mg/kg/day, and there was also an indication of low epididymal weights at this dose. This effect was also seen in the recovery group males. At 750 mg/kg/day, reduced numbers or complete absence of spermatozoa, accompanied by the presence of degenerate spermatogenic cells in the duct(s), were observed in the epididymides and were still present following the 2-week recovery period. Spermatocele granuloma(ta) that was seen in 2 males receiving 750 mg/kg/day and one receiving 60 mg/kg/day was not seen at the end of the recovery period. The significance of this change in the single male receiving 60 mg/kg/day is uncertain as spermatocele granuloma(ta) can occur spontaneously in rats of this age

and considering the absence of other degenerative changes in the testes or epididymides of this animal. Moderate to severe seminiferous tubular atrophy/degeneration was seen in the testes of all animals dosed at 750 mg/kg/day, accompanied by minimal to moderate spermatid giant cells and minimal to slight seminiferous tubular vacuolation. Similar findings were still evident following the 2-week recovery period but at a lower incidence and severity, suggesting a degree of recovery. There were no alterations in the female reproductive cycles or the reproductive organs up to the highest dose tested. Thus, the NOAEL for the fertility endpoint was determined to be 250 mg/kg/day based on impairment of male fertility at 750 mg/kg/day (ECHA, 2013; the ECHA dossier on this material uses terpineol data as read-across).

The most conservative NOAEL of 250 mg/kg/day was selected for the fertility endpoint. Therefore, the terpineol MOE for the fertility endpoint can be calculated by dividing the terpineol NOAEL by the total systemic exposure to 4-carvomenthenol, 250/0.00046, or 543478.

In addition, the total systemic exposure to 4-carvomenthenol (0.46 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1.1. Derivation of reference dose (RfD). Section 5 **provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the**

Table 1
Summary of existing data on α-bisabolol as a read-across for 4-carvomenthenol.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm²	NOEL-HMT (induction) μg/cm²	LOEL[2] (induction) μg/cm²	WoE NESIL[3] μg/cm²	LLNA[4] Weighted Mean EC3[5] Value μg/cm²	GPMT[6]	Buehler[6]
Weak	5509	N/A	N/A	5500	4595 (18.38%) [2]	Positive [1]	Negative [3]
	In vitro Data[7]				*In silico* protein binding alerts (OECD Toolbox v4.6)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Positive [2]	Negative [2]	Positive [1]		No alert found	Radical reactions; SN2	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = Not Available.
[1]WoE 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).
[2]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).
[5]EC3 is the concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation.
[6]Studies conducted according to the OECD TG 406 are included in the table.
[7]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and an RfD of 2 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for inter-species (i.e., between different species) (10 ×) and intraspecies (i.e., between the same species) (10 ×) differences. The RfD for 4-carvomenthenol was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 200 mg/kg/day by the uncertainty factor, 100 = 2 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/17/24.

11.1.4. Skin sensitization

Based on the existing data on the target material and read-across material α-bisabolol, 4-carvomenthenol is a skin sensitizer with a defined NESIL of 5500 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section 10.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for 4-carvomenthenol. Therefore, α-bisabolol (CAS # 515-69-5; see Section 6) was used for the risk assessment of 4-carvomenthenol. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, 4-carvomenthenol is a skin sensitizer. 4-Carvomenthenol and read-across material α-bisabolol are predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.6). 4-Carvomenthenol was found to be borderline and positive in 2 separate *in vitro* direct peptide reactivity assays (DPRA), negative a KeratinoSens, positive in a LuSens, and positive in a human cell line activation test (h-CLAT) (RIFM, 2017a; RIFM, 2018c; RIFM, 2017d; RIFM, 2016c). 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, 4-carvomenthenol is considered a sensitizer. Read-across material α-bisabolol was found to be positive in 2 separate *in vitro* DPRA and an h-CLAT and negative in 2 separate KeratinoSens assays (RIFM, 2016e; ECHA, 2018 [skin sensitization: *in chemico*]; RIFM, 2018a; ECHA, 2018 [skin sensitization: *in vitro*]; RIFM, 2018b, respectively). 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 α-bisabolol is considered a sensitizer. In 2 separate murine local lymph node assays (LLNA), read-across material α-bisabolol was found to be sensitizing with EC3 values of 18.85 % (4712 μg/cm^2) and 17.9 % (4475 μg/cm^2) (RIFM, 1999b; RIFM, 2010a). In a guinea pig maximization test (intradermal injection: 5 % in peanut oil; topical induction: 100 %; topical challenge: 25 % in 1:1 ethanol:diethyl phthalate [EtOH:DEP]), read-across material α-bisabolol led to skin sensitization reactions (RIFM, 1998a). In 3 separate guinea pig Buehler tests ([topical induction and challenge: 0.05 % in peanut oil]; [topical induction: 50 % in 1:1 EtOH:DEP; topical challenge: 10 % in 1:1 EtOH:DEP]; [topical induction: 100 %; topical challenge: 50 % in Lutrol E 400 DAB]), read-across material α-bisabolol did not present reactions indicative of sensitization (RIFM, 1982; RIFM, 1999a; RIFM, 1999c). In a guinea pig open epicutaneous test, 4-carvomenthenol did not lead to skin sensitization reactions at a concentration of 5 % (Klecak, 1985). In 2 separate human maximization tests, no skin sensitization reactions were observed when 4-carvomenthenol was tested at 3450 μg/cm^2 (RIFM, 1977). Additionally, in a Confirmation of No Induction in Humans (CNIH) test with 5509 μg/cm^2 of read-across material α-bisabolol in 3:1 DEP:EtOH, no reactions indicative of sensitization were observed in any of the 107 volunteers (RIFM, 2010b).

Based on weight of evidence (WoE) from structural analysis, *in vitro* studies, animal studies, and human studies on the read-across material as well as the target material, 4-carvomenthenol is a sensitizer with a WoE NESIL of 5500 μg/cm^2 (Table 1). Section 10 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. (2020) and an RfD of 2 mg/kg/day.

Additional References: RIFM, 2017c; RIFM, 1998b.

Literature Search and Risk Assessment Completed On: 02/18/25.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, 4-carvomenthenol 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 4-carvomenthenol in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. Based on the lack of absorbance, 4-carvomenthenol does not present a concern for photoirritation 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. Thus, it does not present a concern for photoirritant or photoallergenic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/21/24.

11.1.6. Local respiratory toxicity

There are insufficient inhalation data available on 4-carvomenthenol; however, in an acute, two-week inhalation study for the analog terpineol (CAS # 8000-41-7; see Section 6), a NOAEC of 20 mg/m^3 was reported (ECHA, 2017a).

11.1.6.1. Risk assessment. The calculated chronic inhalation exposure was considered along with toxicological data from the scientific literature to estimate the MOE when used in perfumery. An OECD 413, 13-week inhalation study in CRL:CD rats identified a Lowest Observed Adverse Effect Concentration (LOAEC) of 200 mg/m^3 (ECHA, 2017a; uses terpineol data as read-across). In this study, 10 rats/sex/group were exposed to terpineol via nose-only inhalation for 6 h a day, 5 days per week for 13 weeks. The test concentrations were 0, 200, 600, and 2000 mg/m^3. Standard evaluations included mortality, clinical observations, body weight, hematology, clinical chemistry, and gross and microscopic pathology. After 13 weeks of treatment, related effects were observed in the nasal turbinates and nasal pharynx. Minimal to slight severity hyperplasia of the mucous cells in nasal turbinates was observed in males from all the terpineol exposure groups (0/10, 9/10, 9/10, 10/10) and the females from all the terpineol exposure groups (0/10, 4/10, 8/10, 8/10). Minimal degeneration of olfactory epithelium, respiratory epithelium, and inflammation of the respiratory epithelium in the nasal turbinates was observed in the males and females of the high-dose group. Minimal hyperplasia of the mucous cells in the nasal pharynx was observed in the males and females of the mid- and high-dose groups. Based on the observations in the respiratory tract, the LOAEC is identified at 200 mg/m^3. Therefore, by using a safety adjustment factor of 10, a local effects NOAEC of 20 mg/m^3 is calculated for the subchronic inhalation exposure of terpineol.

This NOAEC expressed in mg/kg lung weight/day is.

- (20 mg/m^3) × (1m^3/1000L) = 0.02 mg/L
- Minute ventilation of 0.17 L/min* for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.02 mg/L) × (61.2 L/d) = 1.224 mg/day

- (1.224 mg/day)/(0.0016 kg lung weight of rat**) = 765 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0022 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight to give 0.0034 mg/kg lung weight/day, resulting in a MOE of 225000 (i.e., [765 mg/kg lung weight of rat/day]/[0.0034 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species (i.e., between different species) variation (× 10) and intra-species (i.e., within the same species) variation (× 10), the material exposure by inhalation at 0.0022 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms and Travis (1988).

**Phalen (2009).

Additional References: Rice, 1994a; Regnault-Roger and Hamraoui, 1995; Rice, 1994b

Literature Search and Risk Assessment Completed On: 08/23/24.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4-carvomenthenol 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 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 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, 4-carvomenthenol 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) did not identify 4-carvomenthenol 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, 2017b). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current VoU (IFRA, 2019), 4-carvomenthenol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. RIFM, 2001a: Biodegradation of 4-carvomenthenol was evaluated according to the OECD 301D method. 3.0 mg/L of the test material was incubated for 28 days. A maximum of 69 % biodegradation was observed after 21 days.

11.2.3.2. Ecotoxicity. RIFM, 2001b: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The test material concentrations were calculated based on DOC analysis. The 48-h EC50 value was reported to be 6.3 mg/L.

RIFM, 2000a: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 97 mg/L.

RIFM, 2017b: The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions in a closed system without headspace. The 72-h EC50 values based on mean measured concentrations for yield and growth rate were reported to be 11.0 mg/L and 20.6 mg/L, respectively.

11.2.4. Other available data

4-Carvomenthenol has been registered for REACH with additional data (ECHA, 2023):

A 48-h static acute *Daphnia magna* toxicity test was conducted in accordance with OECD 202 guidelines. The reported EC50 was 81.3 mg/L and was based on nominal concentrations.

According to the OECD 201 guidelines, a 72-h acute algae growth inhibition test was conducted on *Raphidocelis subcapitata* in static conditions. The growth rate EC50 was reported as 36.9 mg/L and was based on the geometric mean measured concentrations.

A CO_2 evaluation test was conducted in accordance with OECD 301B guidelines to determine the biodegradability of 4-carvomenthenol. On day 28, a biodegradation of 95 % was observed.

11.2.5. Risk assessment refinement

Because 4-carvomenthenol has passed the screening criteria for risk, measured data are included for completeness only and have not been used for PNEC calculations.

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	3.33	3.33
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	1–10	1–10
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 0.518 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	14.49			1000000	0.0144	
ECOSAR Acute Endpoints **(Tier 2)** v2.0	8.068	5.18	6.416	10000	0.518	Neutral Organics

Literature Search and Risk Assessment Completed On: 08/20/24.

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
- **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 05/27/25.

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.2025.115646.

Appendix

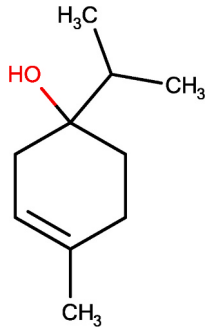
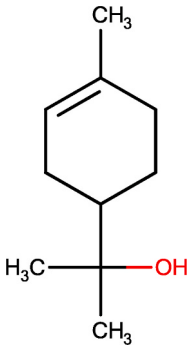
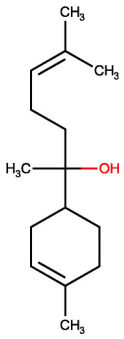
Read-across Justification:

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, 2017c).

- 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 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 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.

	Target Material	Read-across Material	Read-across Material
Principal Name	4-Carvomenthenol	Terpineol	α-Bisabolol
CAS No.	562-74-3	8000-41-7	515-69-5
Structure			
Similarity (Tanimoto Score)		0.78	0.76
SMILES	CC(C)C1(O)CCC(C)=CC1	CC1CCC(CC = 1)C(C)(C)O	CC(C)=CCCC(C)(O)C1CCC(C)=CC1
Endpoint		Repeated dose toxicity Reproductive toxicity Local respiratory toxicity	Skin sensitization
Molecular Formula	$C_{10}H_{18}O$	$C_{10}H_{18}O$	$C_{15}H_{26}O$
Molecular Weight	154.253	154.253	222.372
Melting Point (°C, EPI Suite)	14.86	33.00	55.96
Boiling Point (°C, EPI Suite)	209.00	217.50	299.83
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.69E+00	2.61E+00	1.81E-02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.87E+02	1.98E+03	1.69E+00
Log KOW	3.26	3.28	5.63
J_{max} (μg/cm^2/h, SAM)	39.41	205.45	0.27
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.60E+00	2.26E-01	6.85E+00
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized	Not categorized	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.6)	Non-binder, impaired OH or NH2 group	Non-binder, without OH or NH2 group	
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)	Toxicant (good reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found		No alert found
Protein Binding (OECD)	No alert found		No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found		No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified		No skin sensitization reactivity domain alerts identified
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.6)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 4-carvomenthenol (CAS # 562-74-3). 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, terpineol (CAS # 8000-41-7) and α-bisabolol (CAS # 515-69-5) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Terpineol (CAS # 8000-41-7) was used as a read-across analog for the target material 4-carvomenthenol (CAS # 562-74-3) for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the group of tertiary alcohols with a monocyclic ring with unsaturation.
  - o The key difference between the target material and the read-across analog is that the target material contains the tertiary alcohol directly on the ring. 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 target material nor read-across analog contains *in silico* alerts for repeated dose toxicity. The data from the repeated dose toxicity section confirms that the MOE of the target material is adequate under the current usage. Therefore, the lack of alerts is consistent with the data.
  - o Both the target material and read-across analog contain *in silico* alerts for non-binder and toxicant (developmental toxicity and fertility). The data from the reproductive toxicity section confirms that the MOE of the target material is adequate under the current usage. As a result, the predictions are superseded by the data.
  - o The data described in the local respiratory toxicity sections confirm that the MOE for the read-across analogs is adequate under the current usage. Therefore, based on the structural similarity between the target material and the read-across analogs, the data is considered and applied to the target material.
  - 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.
- α-Bisabolol (CAS # 515-69-5) was used as a read-across analog for the target material 4-carvomenthenol (CAS # 562-74-3) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the group of tertiary alcohols with a monocyclic ring with unsaturation.
  - o The key difference between the target material and the read-across analog is that the target material contains the tertiary alcohol directly on the ring. Additionally, the read-across analog has an additional isolated vinylene on a side chain. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.6, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Neither the target material nor read-across analog contains *in silico* alerts for skin sensitization. The data from the skin sensitization section indicates that the read-across analog is a weak sensitizer. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the lack of alerts is superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification:

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

Q1. 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 detailed explanation). Yes. Class Low (Class I).

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