Food and Chemical Toxicology 163 (2022) 113059

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

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

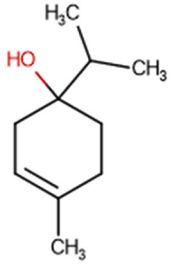
A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], M. Date [a], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H.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

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

ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 121421. This safety assessment is an updated version and replaces the previous version at https://doi.org/10.1016/j.fct.2017.07.040 (RIFM, 2017d)**. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here:** fragrancematerialsafetyresource.elsevier.com**.**



Name: 4-Carvomenthenol

(*continued on next column*)

(*continued*)

CAS Registry Number: 562-74-3

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
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.,

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2022.113059
Received 15 December 2021; Accepted 16 April 2022
Available online 20 April 2022
0278-6915/

(*continued*)

2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

4-Carvomenthenol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/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 and reproductive toxicity endpoints. Data show that there are no safety concerns for 4-carvomenthenol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 4-carvomenthenol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 4-Carvomenthenol is below the TTC (1.4 mg/day). 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, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2000b; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 578 mg/kg/day.	(ECHA REACH Dossier: 4-(1-Methoxy-1-methylethyl)-1-methylcyclohexene; ECHA, 2017a; uses terpineol data as read-across)
Reproductive Toxicity: Developmental toxicity: NOAEL = 200 mg/kg/day. Fertility: NOAEL = 250 mg/kg/day.	(ECHA REACH Dossier: 4-(1-Methoxy-1-methylethyl)-1-methylcyclohexene; ECHA, 2017a; uses terpineol data as read-across)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(RIFM, 2017a; RIFM, 2017c; RIFM, 2016c)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 69% (OECD 301D)	RIFM (2001a)
Bioaccumulation: Screening-level: 65.76 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 5.18 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 5.18 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.518 μg/L	
• Revised PEC/PNECs (2015 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; ﾃﾙﾋﾟﾈﾝ-4-ｵｰﾙ; 1-Isopropyl-4-methylcyclohex-3-en-1-ol; Terpinenol-4 NAT; Terpinenol-4 Pure; 4-Carvomenthenol
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25 g/mol
6. **RIFM Number:** 932
7. **Stereochemistry:** Stereiosimer not specified. One chiral center and a total of 2 enantiomers are possible.

2. Physical data

1. **Boiling Point:** 89 °C at 6 mm Hg (Fragrance Materials Association [FMA]), 211.85 °C (EPI Suite), 214–219 °C (corrected to normal atmospheric pressure of 1013 hPa) (RIFM, 2016b)
2. **Flash Point:** 82 °C (Globally Harmonized System), 179 °F; CC (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)
4. **Melting Point**: 14.86 °C (EPI Suite), −21 to −23 °C (at atmospheric pressure of 991 hPa or 1012 hPa, respectively) (RIFM, 2016b)
5. **Water Solubility:** 386.6 mg/L (EPI Suite)
6. **Specific Gravity:** 0.936 (FMA)

7. **Vapor Pressure:** 0.02 mm Hg at 20 °C (FMA), 0.0263 mm Hg at 20 °C (EPI Suite v4.0), 0.0427 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid that is very slightly soluble in water, 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).

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.2)

1. **95**th **Percentile Concentration in Fine Fragrance** 0.010% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.000022 mg/kg/day or 0.0016 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00043 mg/kg/day (RIFM, 2018)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

*See the Appendix below for further 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:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   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*:

Apple fresh (*Malus* species)	Chamomile
Beans	Dill (*Anethum* species)
Grape (*Vitis* species)	Peanut (*Arachis hypogaea* L.)
	Soybean (*Glycine max*. L. merr.)
Honey	Tea
Malt	

*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; accessed 12/14/21 (ECHA, 2017a).

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, 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. 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 (DRF) 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: 06/04/21.

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 VI) 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 MMAD was between 0.52 and 1.6 μM, and the respective 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 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 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 administration of volatile hydrocarbons and are of no consequence to human risk assessment (Lehman-McKeeman and Caudill, 1992 and 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, 2017a; 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, 578/0.00043, or 1344186.

In addition, the total systemic exposure to 4-carvomenthenol (0.43 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: 05/19/21.

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, 2017a; 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, 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, 2017a; 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 terpineol, 200/0.00043 or 465116.

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, 2017a; 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 terpineol, 250/0.00043, or 581395.

In addition, the total systemic exposure to terpineol (0.43 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/21.

11.1.4. Skin sensitization

Based on the existing data, 4-carvomenthenol does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, 4-carvomenthenol is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 4-Carvomenthenol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens, but positive in the human cell line activation test (h-CLAT) (RIFM, 2017a; RIFM, 2017c; RIFM, 2016c). In an open epicutaneous test in guinea pigs, no reactions indicative of skin sensitization were observed with 4-carvomenthenol (Klecak, 1985). Additionally, in 2 human maximization tests, no reactions indicative of sensitization were observed with 5% (3450 μg/cm^2) 4-carvomenthenol in petrolatum (RIFM, 1977).

Based on the weight of evidence (WoE) from structural analysis and *in vitro,* animal, and human studies, 4-carvomenthenol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

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

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, 4-carvomenthenol would not be expected to present a concern for phototoxicity or photoallergenicity.

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

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

Additional References: None.

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

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4-carvomenthenol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on 4-carvomenthenol. Based on the Creme RIFM Model, the inhalation exposure is 0.0016 mg/day. This exposure is 875 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

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

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 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 risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 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 persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 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. The biodegradation reached the pass level of >60% after 8 days and came to a maximum of 69% 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 8.2 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 with the 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 no additional data at this time.

11.2.5. Risk assessment refinement

Because 4-carvomenthenol has passed the screening criteria for risk, measured data is included for completeness only and has 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.

11.2.6. 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 Volume of Use 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.

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

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/

	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)** v1.11	8.068	5.18	6.416	10000	0.518	Neutral Organics

- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 12/14/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113059.

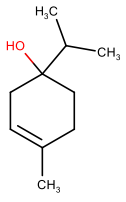
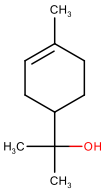
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 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 v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	4-Carvomenthenol	Terpineol
CAS No.	562-74-3	8000-41-7
Structure		
Similarity (Tanimoto Score)		0.78
SMILES	CC(C)C1(O)CCC(C) = CC1	CC1CCC(CC = 1)C(C) (C)O
Endpoint		Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_{10}H_{18}O$	$C_{10}H_{18}O$

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Molecular Weight (g/mol)	154.253	154.253
Melting Point (°C, EPI Suite)	14.86	33.00
Boiling Point (°C, EPI Suite)	209.00	217.50
Vapor Pressure (Pa @ 25 °C, EPI Suite)	5.69E+00	2.61E+00
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	3.87E+02	1.98E+03
Log K_{OW}	3.26	3.28
J_{max} (μg/cm^2/h, SAM)	39.41	205.45
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.60E+00	2.26E-01
Repeated Dose Toxicity		
Repeated Dose (HESS)	Not categorized	Not categorized
Developmental and Fertility Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	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)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 4-carvomenthenol (CAS # 562-74-3). Hence *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, terpineol (CAS # 8000-41-7) was identified as a read-across material with data for its respective toxicity endpoints.

Conclusion

- Terpineol (CAS # 8000-41-7) could be used as a structurally similar read-across analog for the target material 4-carvomenthenol (CAS # 562-74-3) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of unsaturated cyclic tertiary terpene alcohols.
  - o The target material and the read-across analog have a cycloalkene (2-(4-methylcyclohex-3-en-1-yl)propan-2-ol) fragment common among them.
  - o The key difference between the target material and the read-across analog is that the target material has isopropyl branching near the hydroxy group while the read-across analog has 2 methyl groups flanking the hydroxy group. This makes the target material's hydroxy group more sterically hindered compared to the hydroxy group in the read-across analog. 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 QSAR OECD Toolbox (v4.2), structural alerts for the skin sensitization, repeated dose, and reproductive endpoints are consistent between the target material and the read-across analog. The CAESAR model v.2.1.6 predicts the target and the read-across analog to be sensitizers. Other protein binding alerts for both of the substances are negative. The data described in the skin sensitization section above shows that the read-across analog does not pose a concern for the skin sensitization endpoint. Therefore, this alert will be superseded by the availability of data. In addition, the target material and read-across analog are predicted to be a toxicant for the developmental endpoint with good reliability only by the CAESAR model v.2.1.6. The data described in the developmental and reproductive section supports that the read-across material is safe to use within a given MOE and level of use for developmental toxicity endpoint, so these *in silico* predictions will be superseded.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator. Due to structural differences and more steric hindrance, the target material shows a fewer number of metabolic transformations compared to the read-across analog, which increases *in vivo* reactivity of the read-across analog.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant for the skin sensitization, repeated dose, developmental, and reproductive endpoints.

Explanation of Cramer Classification

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

Q1. 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
Q43. Possibly harmful divalent sulfur (not detected via Q3) No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q42. Possibly harmful analog of benzene No
Q7. Heterocyclic? No
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation) No
Q17. Readily hydrolyzed to a common terpene? Yes

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

References

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

Arctander, S., 1969. Perfume and Flavor Chemicals (Aroma Chemicals), vols. I and II. Published by the author: Montclair, NJ (USA).

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

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

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

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

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

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

ECHA, 2012. Guidance on information requirements and chemical safety assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2017a. 4-(1-Methoxy-1-methylethyl)-1-methylcyclohexene registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/19241/1/2.

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

Hall, A.P., Elcombe, C.R., Foster, J.R., Harada, T., Kaufmann, W., et al., 2012. Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes–conclusions from the 3rd International ESTP expert workshop. Toxicol. Pathol. 40 (7), 971–994.

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

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

Klecak, G., 1985. The Freund's complete Adjuvant test and the open epicutaneous test. Curr. Probl. Dermatol. 14, 152–171.

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

Lehman-McKeeman, L.D., Caudill, D., 1992. a-2u-globulin is the only member of the lipocalin protein superfamily that binds to hyaline droplet inducing agents. Toxicol. Appl. Pharmacol. 116 (2), 170–176.

Lehman-McKeeman, L.D., Rivera-Torres, M.I., Caudill, D., 1990. Lysosomal degradation of alpha2u-globulin and alpha2u-globulin-xenobiotic conjugates. Toxicol. Appl. Pharmacol. 103 (3), 539–548.

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

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

Regnault-Roger, C., Hamraoui, A., 1995. Fumigant toxic activity and reproductive inhibition induced by monoterpenes on Acanthoscelides obtectus (Say) (Coleoptera), a bruchid of kidney bean (Phaseolus vulgaris L.). J. Stored Prod. Res. 31 (4), 291–299.

Rice, P.J., Coats, J.R., 1994a. Insecticidal properties of several monoterpenoids to the house fly (Diptera: muscidae), red flour beetle (Coleoptera: tenebrionidae) and southern corn rootworm (Coleoptera: chrysomelidae). J. Econ. Entomol. 87 (5), 1172–1179.

Rice, P.J., Coats, J.R., 1994b. Insecticidal properties of monoterpenoid derivatives to the house fly (Diptera; Muscidae) and red flour beetle (Coleoptera: tenebrionidae). Pestic. Sci. 41 (3), 195–202.

RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1691.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000a. 4-Carvomenthenol (4-terpinenol): Acute Immobilisation Test (48 H) to Daphnia Magna STRAUS. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Dragoco Gerberding and Co. GmbH. RIFM report number 37731.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000b. 4-Carvomenthenol (Terpinenol-4): Reverse Mutation Assay with Salmonella typhimurium. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 54983.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. 4-Carvomenthenol (Terpinenol-4): Ready Biodegradability Closed Bottle Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 54984.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. 4-Carvomenthenol (Terpinenol-4): Acute Immobilisation Test (48 H) to Daphnia Magna STRAUS. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 60092.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of 4-carvomenthenol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 65419.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015. 4-Carvomenthenol: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 68524.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. 4-Carvomenthenol (Terpinenol-4 Nat): Determination of Physico-Chemical Properties Flash Point. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from RIFM report number 70816.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. 4-Carvomenthenol (Terpinenol-4 Nat): Determination of Physico-Chemical Properties Melting Point and Boiling Point. RIFM, Woodcliff Lake, NJ, USA. . Unpublished report from RIFM report number 70818.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016c. 4-Carvomenthenol (4-terpinenol): in Vitro Skin Sensitization Test - Human Cell Line Activation Test (H-CLAT). RIFM, Woodcliff Lake, NJ, USA. . Unpublished report from RIFM report number 71209.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017a. 4-Carvomenthenol (Terpinenol-4 NAT): Direct Peptide Reactivity Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 72216.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017b. 4-Carvomenthenol (Terpinenol-4 NAT): Alga, Growth Inhibition Test with Pseudokirchneriella Subcapitata, 72 Hours. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 72217.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017c. 4-Carvomenthenol: in Vitro Skin Sensitisation: ARE-Nrf2 Luciferase Test Method (KeratinoSens™). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 72660.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017d. RIFM fragrance ingredient safety assessment, 4-Carvomenthenol, CAS Registry Number 562-74-3, 2017 Dec Food Chem Toxicol. 110 (Suppl. 1), S403–S411.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Exposure Survey 22, November 2018.

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

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

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

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

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

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

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

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

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

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