Food and Chemical Toxicology 110 (2017) S403–S411

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment, 4-Carvomenthenol, CAS Registry Number 562-74-3

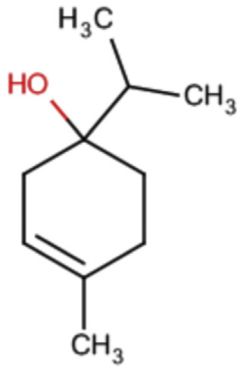
A.M. Api [a, *], D. Belsito [b], D. Botelho [a], D. Browne [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], K. Joshi [a], S. La Cava [a], A. Lapczynski [a], D.C. Liebler [i], D. O'Brien [a], R. Parakhia [a], A. Patel [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], D. Salvito [a], T.W. Schultz [k], I.G. Sipes [l], Y. Thakkar [a], Y. Tokura [m], S. Tsang [a], J. Wahler [a]

[a] Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA
[b] Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA
[c] Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo SE-20502, Sweden
[d] Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA
[e] Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany
[f] Member RIFM Expert Panel, 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
[g] Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany
[h] Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA
[i] Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN 37232-0146, USA
[j] Member of RIFM Expert Panel, 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
[k] Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996- 4500, USA
[l] Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, USA
[m] Member RIFM Expert Panel, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan

ARTICLE INFO

Article history:
Received 17 April 2017
Received in revised form
7 July 2017
Accepted 20 July 2017
Available online 23 July 2017

Version: 041717. This version replaces any previous versions.
Name: 4-Carvomenthenol
CAS Registry Number: 562-74-3



Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic

(*continued on next page*)

* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

http://dx.doi.org/10.1016/j.fct.2017.07.040

(*continued*)

estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017) compared to a deterministic aggregate approach.

DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

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

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

Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data on the target material and the suitable read across material terpineol (CAS # 8000-41-8) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose, developmental and reproductive toxicity endpoints were completed using terpineol (CAS # 8000-41-7) as a suitable read across analogue, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2000a,b; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 578 mg/kg/day (ECHA REACH Dossier: Terpineol)
Developmental Toxicity: NOAEL = 200 mg/kg/day and **Reproductive Toxicity:** NOAEL = 250 mg/kg/day (ECHA REACH Dossier: Terpineol)
Skin Sensitization: Not sensitizing. (ECHA REACH Dossier: Terpineol; RIFM, 1964)

(*continued*)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
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,b)
Bioaccumulation: Screening Level: 65.76 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48 h *Daphnia magna* LC50: 5.18 mg/l (EpiSuite ver 4.1)
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 (EpiSuite ver 4.1)
RIFM PNEC is: 0.518 μg/L
- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1

1. Identification

1 **Chemical Name:** 4-Carvomenthenol
2 **CAS Registry Number:** 562-74-3
3 **Synonyms:** 4-Carvomenthenol; 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
4 **Molecular Formula:** $C_{10}H_{18}O$
5 **Molecular Weight:** 154.25
6 **RIFM Number**: 932

2. Physical data

1 **Boiling Point:** 89 °C @ 6 mm Hg [FMA database], (calculated) 211.85 °C [EPI Suite]
2 **Flash Point:** 179 °F; CC [FMA database]
3 **Log K_{OW}:** 3.33 [EPI Suite]
4 **Melting Point:** 14.86 °C [EPI Suite]
5 **Water Solubility:** 848 mg/l at 20 ± 2 °C [RIFM, 2000b]; (calculated) 386.6 mg/L [EPI Suite]
6 **Specific Gravity:** 0.936 [FMA database]
7 **Vapor Pressure:** 0.02 mm Hg 20 °C [FMA database], 0.0263 mm Hg @ 20 °C [EPI Suite 4.0], 0.0427 mm Hg @ 25 °C [EPI Suite]
8 **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$)
9 **Appearance/Organoleptic:** A colorless liquid with a warm-peppery, mildly earthy, musty, and woody odor of moderate tenacity. The taste is rather bitter at concentrations higher than 100 ppm while it becomes quite pleasant, warm, herbaceous, and peppery below 50 ppm.

3. Exposure

1 **Volume of Use (worldwide band):** 10 to 100 metric tons per year (IFRA, 2011)
2 **95th Percentile Concentration in Hydroalcoholics:** 0.0051% (RIFM, 2014)
3 **Inhalation Exposure*:** 0.000019 mg/kg/day or 0.0014 mg/day (RIFM, 2014)
4 **Total Systemic Exposure**:** 0.00025 mg/kg/day (RIFM, 2014)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 and Safford et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

*See Appendix below for explanation.

2 **Analogs Selected:**
- a **Genotoxicity:** None
- b **Repeated Dose Toxicity:** Terpineol (CAS # 8000-41-7)
- c **Developmental and Reproductive Toxicity:** Terpineol (CAS # 8000-41-7)
- d **Skin Sensitization:** Terpineol (CAS # 8000-41-7)
- e **Phototoxicity/Photoallergenicity:** None
- f **Local Respiratory Toxicity:** None
- g **Environmental Toxicity:** None

3 **Read-across Justification:** See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

4-Carvomenthenol is reported to occur in the following foods* and in some natural complex substances (NCS):

Acerola (Malpighia)Alpinia speciesAngelica (Angelica archangelica L.)Anise (Pimpinella anisum L.)Anise brandyAannato (Bixa orellana L.)Apple brandy (Calvados)Apple fresh (Malus species)Apple processed (Malus species)Apricot (Prunus armeniaca L.)Ashanti pepper (Piper guineense Schum and Thom)Babaco fruit (Carica pentagona Heilborn)BeansBeerBeli, bael (Aegle marmelos Correa) Black currants (Ribes nigrum L.)Buchu oilBuckwheatBullock's heart (Annona reticulata L.)Calabash nutmeg (Monodora myristica Dunal) Calamus (sweet flag) (Acorus calamus L.)CamomileCape gooseberry (Physalis peruviana L.)Capsicum speciesCaraway (Carum carvi L.) Cardamom (Ellettaria cardamomum Maton.)Carrot (Daucus carota L.)Celery (Apium graveolens L.)Cherimoya (Annona cherimolia Mill.) CherryChickenChinese quince (Pseudocydonia sinensis Schneid) Cinnamomum speciesCitrus fruitsCloves (Eugenia caryophyllata Thunberg)Cocoa Coriander seed (Coriandrum sativum L.)Cumin seed (Cuminum cyminum L.)Curcuma speciesCurry (Bergera koenigii L.) Custard apple, atemoya (Annona atemoya)Date (Phoenix dactylifera L.)Dill (Anethum species)Elderberry (Sambucus nigra L.)Eucalyptus oil (Eucalyptus globulus Labill)Fennel (Foeniculum vulg., ssp. capillaceum; var.)Filbert, hazelnut (Corylus avellano)GinGinger (Zingiber species)Grape (Vitis species)Grape brandyGuava and feyoaGuava wineHoneyHop (Humulus lupulus)Juniperus communisKiwifruit (Actinidia chinensis, syn. A. deliciosa)Laurel (Laurus nobilis L.)Lemon balm (Melissa officinalis L.)Licorice (Glycyrrhiza glabra L.)Litchi (Litchi chinensis Sonn.)Litchi wineLoganberry (Rubus ursinus var. loganobaccus)Lovage (Levisticum officinale Koch)Mace (Myristica fragrans Houttuyn)MaltMammee apple (Mammea americana L.) Mangifera speciesMastic (Pistacia lentiscus)Mentha oilsMountain papaya (C. candamarcensis, C. pubescens)Myrtle (Myrtus communis L.)NectarineNutmeg (Myristica fragrans Houttuyn)Ocimum speciesOlive (Olea europaea)Omija fruit (Schisandra chinensis Baillon) Origanum (Spanish) (Coridothymus cap.(L.) Rchb.)Papaya (Carica papaya L.)Parsley (Petroselium species)Passion fruit (passiflora species)Peanut (Arachis hypogaea L.)Pecan (Carya illinoensis Koch)Pepino fruit (Solanum muricatum)Pepper (Piper nigrum L.)Pimento (allspice) (Pimenta dioica L. Merr.)Pineapple (Ananas comosus)Pistachio oil (Pistacia vera)Pistacia atlanticaPistacia palaestina (Pistacia terebinthus L.)Plum (Prunus species)Pomegranate juice (Punica granatum L.)Pomegranate wine (Punica granatum L.)Quince, marmelo (Cydonia oblonga Mill.)Raspberry brandyRaspberry, blackberry and boysenberryRed currants (Ribes rubrum L.)Rosemary (Rosmarinus officinalis L.)Salvia speciesSatureja speciesSherrySoybean (Glycine max. L. merr.)Star aniseStarfruit (Averrhoa carambola L.) Sweet grass oil (Hierochloe odorata)Sweet marjoram (Origanum majorana L.)Sweetsop, sugar apple (Annona squamosa L.)Syzygium speciesTamarind (Tamarindus indica L.)Tarragon (Artemisia dracunculus L.)TeaTequila (Agave tequilana)Thyme (Thymus species) Tomato (Lycopersicon esculentum Mill.)Turpentine oil (Pistacia terebinthus)Vacciunium speciesVanillaWater yam (Dioscorea alata) Wild marjoram (Origanum vulgare L.)WineWormwood oil (Artemisia absinthium L.)Xylopia species.

*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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH Dossier

Pre-Registered for 2010; No dossier available as of 04/17/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. 4-Carvomenthenol was tested for genotoxic potential in the BlueScreen assay and was found negative for

both cytotoxicity and genotoxicity indicating a lack of genotoxic concern (RIFM, 2013). Furthermore, the mutagenic potential of 4-carvomenthenol, was tested in a GLP bacterial reverse mutation assay in accordance with OECD TG 471. S. typhimurium strains TA1535, TA97a, TA98, TA100 and TA102 were treated with 4-carvomenthenol in DMSO (dimethyl sulfoxide) with and without metabolic activation (S9) at the concentrations of 0.016–1.6 mg/plate for T97, 0.016–5 mg/plate for TA98 and TA102, and 0.016–1.6 mg/plate (without S9) and 0.016–5 mg/plate (with S9) for strains TA 100 and TA1535. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2000a,b). Under the conditions of the study, the test material was found to have no mutagenic effects.

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 presence and absence of metabolic activation (S9) at the 4 h and 24 h time points. 4-Carvomenthenol did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2015). Under the conditions of the study, 4-carvomenthenol was considered to be non-clastogenic in the in vitro micronucleus test.

Based on all of the above, 4-carvomenthenol does not present a concern for genetic toxicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/01/16.

10.1.2. Repeated dose toxicity

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

10.1.2.1. 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 5) 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 were 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. 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, REACH Dossier on terpineol). 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 five consecutive weeks. An additional 10 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for five weeks and then given two weeks of recovery before termination. The repeated dose toxicity NOAEL was determined to be 750 mg/kg/day, the highest dose tested. 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. 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. There were adverse findings related to treatment with test material on the male reproductive parameters reported among the animals of the high dose group. However the effects on the male reproductive system and organs will be discussed in the reproductive toxicity section of the safety assessment (ECHA REACH Dossier: terpineol). In another study, terpineol multiconstituent No. 2 was administered to 10 male Sprague-Dawley rats for 90 days via diet. The test item was dissolved in corn oil, mixed in Ssniff powder feed at the dose level of 12000 ppm (equivalent to 622.65 mg/kg bw/day) and fed to male Sprague-Dawley rats (10/dose) daily ad libitum for 13 weeks. The body weights were significantly reduced in rats receiving test item at 12000 ppm. This decrease was associated with a decrease in the food intake throughout the treatment period. There was no other test material related adverse effect reported among the treated males (ECHA, REACH Dossier on terpineol). 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, 578/0.00025 or 2,312,000.

In addition, the total systemic exposure to 4-carvomenthenol (0.25 μg/kg/day) is below the TTC (30 μg/kg bw/day) 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: 11/3/16.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 4-carvomenthenol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. 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 five consecutive weeks. An additional 10 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for five weeks and then given two weeks of recovery before termination. There were no adverse effects towards 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. 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 bw/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, REACH dossier on terpineol). 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, 200/0.00025 or 8,000,000.**

In addition, the total systemic exposure to terpineol (0.25 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

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 five consecutive weeks. An additional 10 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for five weeks and then given two 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 duct(s) were observed in the epididymides and were still present following the 2-week recovery period. Spermatocele granuloma(ta) that were seen in two males receiving 750 mg/kg/day and one receiving 60 mg/kg/day were 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 reproductive toxicity endpoint was determined to be 250 mg/kg/day based on impairment of male fertility at 750 mg/kg/day (ECHA, REACH Dossier on terpineol). In another investigatory study, succeeding the OECD 422 screening test, was performed to compare the toxicity of terpineol to the male reproductive system when administered by dietary or oral gavage routes. Three groups of Crl:CD(SD) male rats (five/dose) were administered terpineol daily by dietary and/or oral gavage routes at the following doses:

Group 1: dietary 7500 ppm + supplementary gavage dose 300 mg/kg/day.

Group 2: dietary 10000 ppm + supplementary gavage dose 150 mg/kg/day, and.

Group 3: 750 mg/kg/day by gavage only.

Necropsy data indicated that decreases in reproductive organ weights and changes to macroscopic appearance were most marked in the animals receiving terpineol multiconstituent at 750 mg/kg/day. Sperm analysis showed that motile sperm with normal morphology were present in 4/5 males of Group 2 and 1/5 males of Group 1. The outliers in each group were at the extreme of achieved overall exposure for the group suggesting that absolute exposure was important, although the route of exposure and consequently potential to exceed threshold levels was of greater significance. Microscopic examination indicated there were relatively fewer changes in the testes and epididymides in the animals which were given terpineol multiconstituent by the dietary route with oral gavage supplementation (Groups 1 and 2), whereas there were significant changes in those which received it solely by oral gavage (Group 3). The results of dietary administration suggest that exposure via the dietary route of administration reduces the testicular and sperm toxicity of the test material compared to dosing by oral gavage. The results of this study, in part, support the hypothesis that a high peak plasma level is necessary to induce the observed toxic effects (ECHA, REACH dossier on terpineol). In another repeated dose oral dietary toxicity study terpineol multiconstituent No. 2 was administered to 10 male Sprague-Dawley rats for 90 days. The test item was dissolved in corn oil, mixed in Ssniff powder feed at the dose level of 12000 ppm and fed to male Sprague-Dawley rats (10/dose) daily ad libitum for 13 weeks. Rats in the control group were fed basal diet only without any test item admixtures. Histopathological examination of the testes and the epididymides were carried out. There were no test item-related histological changes observed in the testis and the epididymis. Thus the NOAEL for male reproductive and systemic toxicity was determined to be 12000 ppm (622.65 mg/kg bw/day) or higher the only dose tested (ECHA, REACH dossier on terpineol). The most conservative NOAEL of 250 mg/kg/day was selected for the reproductive toxicity endpoint. **Therefore, the terpineol MOE for the reproductive toxicity endpoint can be calculated by dividing the terpineol NOAEL by the total systemic exposure to terpineol, 250/0.00025 or 1,000,000.**

In addition, the total systemic exposure to terpineol (0.25 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) 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: 11/3/16.

10.1.4. Skin sensitization

Based on the available data and read across to terpineol (CAS # 8000-41-7), 4-carvomenthenol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data and read across terpineol (CAS # 8000-41-7; see Section 5), 4-carvomenthenol does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). However, it should be noted that as cyclic terpenes, these materials could be reasonably anticipated to undergo autoxidation resulting in potentially sensitizing degradation products. In an open epicutaneous test in guinea pigs, no reactions indicative of skin sensitization were observed with 4-carvomenthenol (Klecak, 1985). Similarly, no reactions indicative of sensitization were observed with read across terpineol in guinea pig studies (ECHA Dossier; Klecak, 1979; RIFM, 1982; Ishihara, 1986). Additionally, in human confirmatory studies no reactions indicative of sensitization were observed with 4-carvomenthenol or terpineol (RIFM, 1977; RIFM, 1961; Greif, 1967; RIFM, 1964). Based on weight of evidence from read across, animal and human data 4-carvomenthenol does not present a concern for skin sensitization.

Additional References: RIFM, 1961; Friedrich et al., 2007; Hausen et al., 1999; Klecak, 1979.

Literature Search and Risk Assessment Completed on: 11/15/13.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 4-carvomenthenol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 $L \cdot mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). Based on lack of absorbance, 4-carvomenthenol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/13/16.

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There are limited inhalation data available on 4-carvomethenol. Based on the Creme RIFM model, the inhalation exposure is 0.0014 mg/day. This exposure is 1000 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,b; Regnault-Roger and Hamraoui, 1995

Literature Search and Risk Assessment Completed on: 10/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 4-carvomenthenol was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for 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 EPISUITE ver 4.1 did identify 4-carvomenthenol as being possibly persistent but not bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.2. Risk assessment. Based on current Volume of Use (2011), 4-carvomenthenol does present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 2001a,b: 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.

10.2.4. Ecotoxicity

RIFM, 2001a,b: A 48 h acute *Daphnia magna* immobilization test was conducted according to the OECD 202 I method. Under the condition of this study, the EC50 of the test material was 8.2 mg/l after 24 h and 6.3 mg/l after 48 h.

10.2.5. Other available data

4-Carvomenthenol has been pre-registered for REACH with no additional data at this time.

10.2.5.1. 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.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	14.49 mg/L			1,000,000	0.0144 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	8.068 mg/L	5.18 mg/L	6.416 mg/L	10,000	0.518 μg/L	Neutral Organics

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 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 11/15/13.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

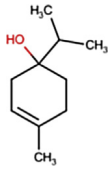
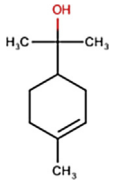
*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

Appendix: Read across justification

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- The Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012)

	Target material	Read across material
Principal Name	3-Cyclohexen-1-ol, 4-methyl-1-(1-methylethyl)-	Terpineol
CAS No.	562-74-3	8000-41-7
Structure		
Similarity (Tanimoto score)[1]		0.38
Read across endpoint		• Skin sensitization • Developmental and Reproductive

(*continued on next page*)

(*continued*)

	Target material	Read across material
		• Repeated dose
Molecular Formula	$C_{10}H_{18}O$	$C_{10}H_{18}O$
Molecular Weight	154.25	154.25
Melting Point (°C, EPISUITE)	14.86	12.36
Boiling Point (°C, EPISUITE)	211.85	214.38
Vapor Pressure (Pa @ 25 °C, EPISUITE)	5.7	2.62
Log Kow (KOWWIN v1.68 in EPISUITE)	3.33	3.33
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	386.6	371.7
J_{max} (mg/cm^2/h, SAM)	1016.613	205.463
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.58E-005	1.58E-005
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	• Non binder, impaired OH or NH_2 group	• Non binder, without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• toxicant (good reliability)	• toxicant (good reliability)
Skin Sensitization		
Protein binding by OASIS v1.1	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	562-74-3 pdf	8000-41-7 pdf

Summary

There are insufficient toxicity data on 3-cyclohexen-1-ol, 4-methyl-1-(1-methylethyl) (CAS # 562-74-3). Hence *in-silico* evaluation was conducted by determining suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analog terpineol (CAS # 8000-41-7) was identified as a proper read across material with data for its respective toxicity endpoints.

Conclusion/rational

- Terpineol (CAS # 8000-41-7) could be used as structurally similar read across analog for the target material 3-cyclohexen-1-ol, 4-methyl-1-(1-methylethyl) (CAS # 562-74-3) for the skin senzitization, repeated dose, developmental and reproductive endpoints.
  - o The target substance and the read across analog are structurally similar and belong to a class of unsaturated cyclic tertiary terpene alcohols.
  - o The target substance 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 substance and the read across analog is that the target substance has isoprypyl branching near the hydroxy group while the read across analog has two methyl groups flanking the hydroxy group. This makes the target substance's hydroxy group more sterically hindered compared to the hydroxy group in the read across analog.
  - o The target substance and the read across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the cycloalkene branched tertiary alcohol fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxic endpoint perspective.
  - o The target substance and the read across analog have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for the skin senzitization, repeated dose, developmental and reproductive endpoints.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for the skin senzitization, repeated dose, developmental and reproductive endpoints are consistent between the target substance 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 skin sensitization endpoint. Therefore this alert will be superseded by the availability of data. In addition, the target and read across analog are predicted to be a toxicant for developmental endpoint with good reliability only by CAESAR model v.2.1.6. The data described in developmental and reproductive section supports that the read across material is safe to use within given margin of exposure and level of use for developmental toxicity endpoint, so this in-silico predictions will be superseded.
  - o The target substance and the read across analog are expected to be metabolized similarly as shown by metabolism simulator. Due to structural differences and more steric hindrance, the target substance shows less 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 substance and the read across analog are deemed to be toxicologically insignificant for the skin senzitization, repeated dose, developmental and reproductive endpoints.

Reason for 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.Normal constituent of the body? **No**
Q2.Contains functional groups associated with enhanced toxicity? **No**
Q3.Contains elements other than C,H,O,N,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 explanation)? **No**
Q17.Readily hydrolysed to a common terpene? **No**
Q19.Open chain? **No**
Q23.Aromatic? **No**
Q24.Monocarbocyclic with simple substituents? **No**
Q25. Cyclopropane, cyclobutane with substituents in Q24 or a mono or bicyclic sulphide or mercaptan? **No**
Q26.Monocycloalkanone or a bicyclocompound? **No**

Q22.Common component of food? **No**
Q33.Has sufficient number of sulphonate or sulphamate groups? **No** Class High (Class III)

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.07.040.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.07.040.

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., Renkers, 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.

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. Central 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.

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

ECHA REACH Dossier: Terpineol: https://echa.europa.eu/home, accessed 4/17/2017.

Essential Estimation Programs Interface (EPI) SuiteTM (version 4.1) [Software]. (Copyright 2000-2011). US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Retrieved from http://www.epa.gov/opptintr/exposure/pubs/episuite.htm Research, 20(6), 482–487.

Friedrich, K., Delgado, I.F., Santos, L.M.F., Paumgartten, F.J.R., 2007. Assessment of sensitization potential of monoterpenes using the rat popliteal lymph node assay. Food Chem. Toxicol. 45 (8), 1516–1522.

Greif, N., 1967. Cutaneous safety of fragrance material as measured by the maximization test. Am. Perfumer Cosmet. 82, 54–57.

Hall, A.P., Elcombe, C.R., Foster, J.R., Harada, T., Kaufmann, W., Knippel, A., Nolte, T., 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.

Hausen, B.M., Reichling, J., Harkenthal, M., 1999. Degradation products of monoterpenes are the sensitizing agents in tea tree oil. Am. J. Contact Dermat. 10 (2), 68–77.

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), 2011. Volume of Use Survey. February 2011.

Ishihara, M., Itoh, M., Nishimura, M., Kinoshita, M., Kantoh, H., Nogami, T., Yamada, K., 1986. Closed epicutaneous test. Skin Res. 28 (Suppl. 2), 230–240.

Klecak, G., 1979. The Open Epicutaneous Test (OET), a Predictive Test Procedure in the Guinea Pig for Estimation of Allergenic Properties of Simple Chemical Compounds, Their Mixtures and of Finished Cosmetic Preparations. International Federation Societies Cosmetic Chemists, 9/18/79.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. In: Problems in Dermatology. Current Problems in Dermatology, vol. 14, pp. 152–171.

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.

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.

OECD, 2012. The OECD QSAR Toolbox, v. 3.1. 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. Pesticide Sci. 41 (3), 195–202.

RIFM (Research Institute for Fragrance Materials, Inc.), 1961. Sensitization and Irritation Studies. Unpublished report from Givaudan Corporation. RIFM report number 14581 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 1964. Repeated Insult Patch Test of Terpineol on Human Skin. Unpublished report from International Flavors and Fragrances. RIFM report number 24193 (RIFM, Woodcliff Lake, NJ, USA.).

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

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Toxicology Studies of Terpineol in the Guinea Pig. Unpublished report from Takasago International Corporation. RIFM report number 35060 (RIFM, Woodcliff Lake, NJ, USA.).

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

RIFM (Research Institute for Fragrance Materials, Inc.), 2000b. 4-Carvomenthenol (Terpinenol-4): Water Solubility. Unpublished report from Symrise. RIFM report number 61549 (RIFM, Woodcliff Lake, NJ, USA.).

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

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

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

RIFM (Research Institute for Fragrance Materials), 2014. Use Level Survey. April 2014.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015. 4-carvomenthenol: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM report number 69543 (RIFM, Woodcliff Lake, NJ, USA.).

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.

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., 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.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An in silico skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.

USEPA, 2012. Estimation Programs Interface Suite™ for Microsoft® Windows. United States Environmental Protection Agency, Washington, DC, USA, v. 4.11. .