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Short Review

RIFM fragrance ingredient safety assessment, terpinyl formate, CAS Registry Number 2153-26-6

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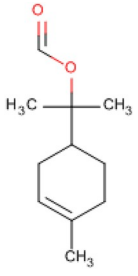
Version: 030618. This version replaces any previous versions.
Name: Terpinyl formate
CAS Registry Number: 2153-26-6



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

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Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.
Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

The material (terpinyl formate) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data on the read-across analog α-terpineol acetate (CAS# 80-26-2) show that terpinyl formate is not genotoxic. Data from the read-across analog terpinyl acetate (isomer mixture; CAS# 8007-35-0) show that terpinyl formate is not a concern for skin sensitization and provided an MOE > 100 for the repeated dose toxicity endpoint. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day, respectively). The developmental and reproductive toxicity endpoint was completed using terpineol (CAS# 8000-41-7) and formic acid (CAS# 64-18-6) as read-across analogs, which provided an MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; terpinyl formate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2014a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 400 mg/kg/day.	(Hagan et al., 1967)
Developmental and Reproductive Toxicity: NOAEL = 200 and 250 mg/kg/day, respectively.	(ECHA Dossier: Terpineol)
Skin Sensitization: Not a concern for skin sensitization.	(RIFM, 2012)
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: Screening-level: 2.63 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 147 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 6.836 mg/L (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 6.836 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.006836 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Terpinyl formate
2. **CAS Registry Number:** 2153-26-6
3. **Synonyms:** 3-Cyclohexene-1-methanol, α,α,4-trimethyl-, formate; p-Menth-1-en-8-yl formate; ｱﾙｶﾝ酸(C = 1 ~ 5)ﾃﾙﾋﾟﾆﾙ; 1-Methyl-1-(4-methylcyclohex-3-en-1-yl)ethyl formate; Terpinyl formate
4. **Molecular Formula:** $C_{11}H_{18}O_2$
5. **Molecular Weight:** 182.26
6. **RIFM Number:** 730
7. **Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 213 °C (FMA), 221.88 °C (EPI Suite)
2. **Flash Point:** 93 °C (GHS), 199°F; CC (FMA)
3. **Log K_{OW}:** 3.79 (EPI Suite)
4. **Melting Point**: 19.12 °C (EPI Suite)
5. **Water Solubility:** 31.13 mg/L (EPI Suite)
6. **Specific Gravity:** 0.990 (FMA)
7. **Vapor Pressure:** 0.0782 mm Hg @ 20 °C (EPI Suite v4.0), 0.03 mm Hg 20C (FMA), 0.119 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless liquid. Very slightly soluble in water; soluble in alcohol and oils. Fresh, floral-citrusy, tart-herbaceous, semi-dry odor of moderate to poor tenacity. Peculiar "astringent-dry" fruity taste, bitter in concentrations higher than 20 ppm. (Arctander Volume II, 1969)

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.000048% (RIFM, 2014c)
3. **Inhalation Exposure*:** 0.000016 mg/kg/day or 0.0011 mg/day (RIFM, 2014c)
4. **Total Systemic Exposure**:** 0.00016 mg/kg/day (RIFM, 2014c)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1 **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
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2. **Analogs Selected**
   a. **Genotoxicity:** α-Terpineol acetate (CAS # 80-26-2)
   b. **Repeated Dose Toxicity:** Terpinyl acetate (isomer mixture; CAS # 8007-35-0)
   c. **Developmental and Reproductive Toxicity:** Terpineol (CAS # 8000-41-7); formic acid (CAS # 64-18-6)
   d. **Skin Sensitization:** Terpinyl acetate (isomer mixture; CAS # 8007-35-0)
   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)

Terpinyl formate is reported to occur in the following foods*:
Cocoa.

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 2/14/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, terpinyl formate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Terpinyl formate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of terpinyl formate. However, read-across can be made to α-terpineol acetate (CAS # 80-26-2; see Section V). The mutagenic activity of α-terpineol acetate 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, and *Escherichia coli* strain WP2uvrA were treated with α-terpineol acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2014a). Under the conditions of the study, α-terpineol acetate was not mutagenic in the Ames test, and this can be extended to terpinyl formate.

There are no studies assessing the clastogenic activity of terpinyl formate. However, read-across can be made to α-terpineol acetate (CAS # 80-26-2; see Section V). α-Terpineol acetate 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 α-terpineol acetate in DMSO at concentrations up to 225 μg/mL in the presence and absence of metabolic activation (S9) at the 3-h and 24-h time points. A statistically significant increase in the frequency of binucleated cells with micronuclei (BNMN) was observed at 58.3 μg/mL in the approximate 24-h treatment in the absence of S9. However, the %BNMN frequency (1.00%) at this concentration was within the historical control range. The percentage of cells with micronucleated binucleated cells in the test-substance tested groups was not significantly increased relative to vehicle control at any dose level for the 3-h treatment in the presence or absence of S9 (RIFM, 2014b). Under the conditions of the study, α-terpineol acetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to terpinyl formate.

Based on the available data, α-terpineol acetate does not present a concern for genotoxic potential, and this can be extended to terpinyl formate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/03/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for terpinyl formate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on terpinyl formate. Read-across material terpinyl acetate (isomer mixture; CAS # 8007-35-0) has a dietary 20-week chronic toxicity study conducted in Osborne-Mendel rats. Groups of 10 rats/sex/dose were administered diets containing 0, 1000, 2500, or 10000 ppm terpinyl acetate (isomer mixture), equivalent to 0, 50, 250, or 500 mg/kg/day, for 20 weeks. No effects on growth, no alterations in hematology, and no macroscopic or microscopic changes were observed up to the highest dose of 10000 ppm. The animals exposed to 10000 ppm in the diet consumed between 400 and 500 mg/kg/day terpinyl acetate. Thus, the NOAEL for repeated dose toxicity was considered to be 10000 ppm or 400 mg/kg/day (Hagan et al., 1967; data also available in Bar and Griepentrog, 1967; and ECHA Dossier: p-menth-1-en-8-yl acetate). Therefore, the terpinyl formate MOE for the repeated dose toxicity endpoint can be calculated by dividing the terpinyl acetate NOAEL in mg/kg/day by the total systemic exposure to terpinyl formate, 400/0.00016 or 2500000.

In addition, the total systemic exposure to terpinyl formate (0.16 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: 07/31/17.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for terpinyl formate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on terpinyl formate. Terpinyl formate is expected to hydrolyze to terpineol (CAS # 8000-41-7; see section V) and formic acid (CAS # 64-18-6; see section V). Formic acid is expected to be oxidized to CO_2 and H_2O in the liver via folate dependent and catalase-peroxidative mechanisms and hence is not likely to contribute to terpinyl formate toxicity.

The metabolite terpineol has an OECD 422 gavage combined repeated dose toxicity study with a reproduction/developmental toxicity screening test conducted in Sprague Dawley rats. The rats were administered via gavage with test material terpineol at doses of 0, 60, 250, or 750 mg/kg/day in corn oil. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at top dose: 5 males/dose). The toxicity subgroup consisted of 5 females/dose and 10 males. 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 towards the development of the fetus up to 250 mg/kg/day. At 750 mg/kg/day, no females became pregnant. It was 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 considered to be 250 mg/kg/day (ECHA Dossier: Terpineol). In another study, terpineol multiconstituent diluted in corn oil was administered by gavage to groups of mated female Sprague Dawley rats (20/dose) at the dose levels of 0, 60, 200, or 600 mg/kg/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 the reduced mean male and female fetal weight at 600 mg/kg/day. In addition, the mean placental weight in this dose group was slightly low with differences attaining statistical significance. Mean placental, litter, and fetal weights at 60 or 200 mg/kg/day were unaffected by maternal treatment with terpineol. The incidence of major and minor abnormalities and skeletal variants showed no relationship to maternal treatment with terpineol. Thus, the NOAEL for the developmental toxicity was considered to be 200 mg/kg/day (ECHA Dossier: Terpineol). The most conservative NOAEL of 200 mg/kg/day was selected for the developmental toxicity endpoint.

Therefore, the terpinyl formate MOE for the developmental toxicity endpoint can be calculated by dividing the terpineol NOAEL in mg/kg/day by the total systemic exposure to terpinyl formate, 200/0.00016 or 1250000.

There are no reproductive toxicity data on terpinyl formate. Terpinyl formate is expected to hydrolyze to terpineol (CAS # 8000-41-7; see section V) and formic acid (CAS # 64-18-6; see section V). The

metabolite, formic acid has an OECD 413 inhalation subchronic 13-week toxicity study conducted on a group of 10 F344/N rats/sex/group. The test material formic acid was administered via whole body inhalation at concentrations of 0, 8, 32, 64, and 128 ppm, equivalent to 0, 4, 17, 34, and 68 mg/kg/day according to standard minute volume and bodyweight parameters for F344/N rats. In addition to the systemic toxicity, the reproductive parameters, i.e. sperm morphology and vaginal cytology, were evaluated for both males and females, respectively. There was no adverse toxicity reported towards the reproductive parameters up to the highest dose tested. The NOAEL for reproductive toxicity was considered to be 128 ppm or 68 mg/kg/day, the highest dose tested (National Toxicology Program, 1992).

The metabolite terpineol has an OECD 422 gavage combined repeated dose toxicity study with a reproduction/developmental toxicity screening test conducted in Sprague Dawley rats. The rats were administered via gavage with test material terpineol at doses of 0, 60, 250, or 750 mg/kg/day in corn oil. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at top dose: 5 males/dose). The toxicity subgroup consisted of 5 females/dose and 10 males. 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. Testis weight was markedly lower in males receiving 750 mg/kg/day (58% of controls), 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 2 males receiving 750 mg/kg/day and 1 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 considered to be 250 mg/kg/day, based on impairment of male fertility at 750 mg/kg/day (ECHA Dossier: Terpineol).

Therefore, the terpinyl formate MOE for the reproductive toxicity endpoint can be calculated by dividing the terpineol NOAEL in mg/kg/day by the total systemic exposure to terpinyl formate, 250/0.00016 or 1562500.

In addition, the total systemic exposure to terpinyl formate (0.16 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/31/17.

10.1.4. Skin sensitization

Based on the existing data on read-across analog terpinyl acetate (isomer mixture) (CAS # 8007-35-0), terpinyl formate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available on terpinyl formate. Based on the available data on read-across analog terpinyl acetate (isomer mixture) (CAS # 8007-35-0; see Section V), terpinyl formate does not present a concern for skin sensitization. The chemical structure of these materials would indicate that they would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v4.1). In a murine local lymph node assay, read-across analog terpinyl acetate (isomer mixture) was found to be negative up to the maximum tested concentration of 100%, which resulted in a Stimulation Index (SI) of 2.4 (RIFM, 2012). In guinea pigs, an open epicutaneous test with read-across analog terpinyl acetate (isomer mixture) did not present reactions indicative of sensitization (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with 2% or 1380 μg/cm^2 terpinyl formate in petrolatum (RIFM, 1975). In a human maximization test, no skin sensitization reactions were observed with 5% or 3450 μg/cm^2 read-across terpinyl acetate (isomer mixture) in petrolatum (RIFM, 1971). Based on weight of evidence from structural analysis, human studies, and read-across analog terpinyl acetate (isomer mixture), terpinyl formate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/07/17.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, terpinyl formate 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 terpinyl formate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, terpinyl formate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available UV/Vis spectra (OECD TG 101) for terpinyl formate indicate no significant absorbance between 290 and 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: 07/07/17.

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on terpinyl formate. Based on the Creme RIFM Model, the inhalation exposure is 0.0011 mg/day. This exposure is 1273 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/03/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of terpinyl formate 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, terpinyl formate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify terpinyl formate as possibly being either persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), terpinyl formate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Terpinyl formate has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.79	3.79
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.006836 μg/L. The revised PEC/PNECs for EU and NA: Not Applicable; cleared at screening-level and therefore, does not present a risk to the aquatic environment at the currently reported volumes of use.

Literature Search and Risk Assessment Completed On: 8/3/17.

11. Literature search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	6.836			1,000,000	0.006836	

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2018.10.013.

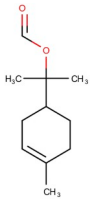
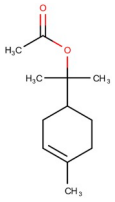
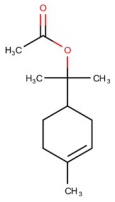
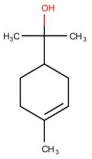
Appendix

Read-across justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- NA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox 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	Terpinyl formate	α-Terpineol acetate	Terpinyl acetate (isomer mixture)	Terpineol	Formic acid
CAS No.	2153-26-6	80-26-2	8007-35-0	8000-41-7	64-18-6
Structure					
Similarity (Tanimoto Score)		0.94	0.94	NA	NA
Read-across Endpoint		• Genotoxicity	• Skin sensitization • Repeated dose	• Developmental and reproductive toxicity	• Developmental and reproductive toxicity
Molecular Formula	$C_{11}H_{18}O_2$	$C_{12}H_{20}O_2$	$C_{12}H_{20}O_2$	$C_{10}H_{18}O$	$C_2H_4O_2$
Molecular Weight	182.26	196.26	196.26	154.25	46.03
Melting Point (°C, EPI Suite)	19.12	21.47	21.47	12.36	−24.95
Boiling Point (°C, EPI Suite)	221.88	238.66	238.66	214.38	100.90
Vapor Pressure (Pa @ 25°C, EPI Suite)	15.9	6.63	6.63	2.62	4.78E+003
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.79	3.96	3.96	3.28	−0.54
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	31.13	18.97	18.97	1980	1000000
J_{max} (mg/cm^2/h, SAM)	65.630	235.584	235.584	205.463	4846.835
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.43E+002	1.04E+002	1.04E+002	1.60E+000	7.60E-002
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• Schiff base formation • Nucleophilic attack			

		• Acylation			
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found			
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)			
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found			
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found			
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found			
Oncologic Classification	• Aldehyde type compound	• Not classified			
Repeated dose toxicity					
Repeated Dose (HESS)	• Not categorized		• Not categorized		
Reproductive and Developmental Toxicity					
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, without OH or NH2			• Non-binder, without OH or NH2	• Non-binder, without OH or NH2
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)			• Toxicant (good reliability)	• Non-toxicant (low 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)	• No alert found		• No alert found		
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	No metabolites

Summary

There are insufficient toxicity data on terpinyl formate (CAS # 2153-26-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, α-terpineol acetate (CAS # 80-26-2), terpinyl acetate (isomer mixture) (CAS # 8007-35-0), terpineol (CAS # 8000-41-7), and formic acid (CAS # 64-18-6) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- α-Terpineol acetate (CAS # 80-26-2) was used as a read-across analog for the target material terpinyl formate (CAS # 2153-26-6) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of terpene esters.
  - o The target substance and the read-across analog share a cyclic unsaturated tertiary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a formate acid fragment and the read-across analog has an acetate fragment. This structural difference is toxicologically insignificant.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cyclic unsaturated tertiary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The read-across analog has an alert for Schiff base formation by DNA binding (model by OASIS). It is also classified as an aldehyde type compound. This shows that the read-across analog is more reactive than the target substance. The data described in the genotoxicity section

shows that the read-across analog does not pose a concern for genetic toxicity. Therefore, the alert will be superseded by the availability of the data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Terpinyl acetate (isomer mixture) (CAS # 8007-35-0) was used as a read-across analog for the target material terpinyl formate (CAS # 2153-26-6) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of terpene esters.
  - The target substance and the read-across analog share a cyclic unsaturated tertiary alcohol fragment.
  - The key difference between the target substance and the read-across analog is that the target substance has a formate acid fragment, and the read-across analog has an acetate fragment. This structural difference is toxicologically insignificant.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cyclic unsaturated tertiary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Terpinyl acetate (isomer mixture) (CAS # 8007-35-0) was used as a read-across analog for the target material terpinyl formate (CAS # 2153-26-6) for the repeated dose toxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of terpene esters.
  - The target substance and the read-across analog share a cyclic unsaturated tertiary alcohol fragment.
  - The key difference between the target substance and the read-across analog is that the target substance has a formate acid fragment, and the read-across analog has an acetate fragment. This structural difference is toxicologically insignificant.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cyclic unsaturated tertiary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Metabolism

Metabolism of the target material terpinyl formate (CAS # 2153-26-6) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). The target material is metabolized to α-terpineol (CAS # 98-55-5) and formic acid (CAS # 64-18-6) in the first step with 0.95 probability. α-Terpineol is an isomer of terpineol (CAS # 8000-41-7). Hence, terpineol (CAS # 8000-41-7) and formic acid (CAS # 64-18-6) can be used as read-across for the target material. Read-across terpineol (CAS # 8000-41-7) and formic acid (CAS # 64-18-6) were out of domain for the *in vivo* rat and out of domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and justification is provided.

- Read-across alcohol terpineol (CAS # 8000-41-7) and read-across acid formic acid (CAS # 64-18-6) are used as read-across analogs for the target ester terpinyl formate (CAS # 2153-26-6) for the reproductive and developmental toxicity endpoint.
  - The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - Structural differences between the target substance and the read-across analog are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - 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 analogs are toxicologically insignificant.
  - According to the QSAR OECD Toolbox v3.4, structural alerts for the endpoints evaluated are consistent between the target substance and the read-across analog.
  - The read-across analog is predicted to be a toxicant by the CAESAR model for developmental toxicity. The data described in the developmental toxicity section above show that the read-across analogs have an adequate margin of exposure at the current level of use. Therefore the alert will be superseded by the availability of the data.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target substance.

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