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Short Review

RIFM fragrance ingredient safety assessment, phytol, CAS Registry Number 150-86-7

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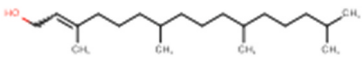

Name: Phytol CAS Registry Number: 150-86-7
Additional CAS Number*:
7541-49-3 2-Hexadecen-1-ol, 3,7,11,15-tetramethyl
*Included because the materials are isomers

Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor

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BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

Phytol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs farnesol (CAS # 4602-84-0) and geraniol (CAS # 106-24-1) show that phytol is not expected to be genotoxic. Data from read-across analog farnesol (CAS # 4602-84-0) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint and a No Expected Sensitization Induction Level (NESIL) of 2700 μg/cm^2 for the skin sensitization endpoint. The reproductive toxicity and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; the exposure to phytol is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; phytol is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; phytol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2008; RIFM, 2010)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day. (Horn et al., 2005)
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: NESIL = 2700 μg/cm^2. RIFM (2004c)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Critical Measured Value: 73% (301F) for CAS # 150-86-7 RIFM (2011)

Bioaccumulation:
Screening-level: 760 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Critical Ecotoxicity Endpoint: 72-h Algae EC50: 1.34 mg/L (ECHA REACH Dossier: (E)-(7R,11R)-3,7,11,15-Tetramethylhexadec-2-ene-1-ol; ECHA, 2017c)

(*continued on next page*)

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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:** 72-h Algae EC50: 1.34 mg/L (ECHA REACH Dossier: (E)-(7R,11R)-3,7,11,15-Tetramethylhexadec-2-ene-1-ol; ECHA, 2017c) **RIFM PNEC is:** 26.8 μg/L • **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe <1

1. Identification

Chemical Name: Phytol	Chemical Name: 2-Hexadecen-1-ol, 3,7,11,15-tetramethyl-
CAS Registry Number: 150-86-7 **Synonyms:** 2-Hexadecen-1-ol, 3,7,11,15-tetramethyl-, [R-[R*,R*-(E)]]-; [R-[R*,R*-(E)]]-3,7,11,15-Tetramethyl-2-hexadecen-1-ol; 脂肪族不飽和アルコール(C = 9 ~ 24); 3,7,11,15-Tetramethylhexadec-2-en-1-ol; *trans*-Phytol; Phytol **Molecular Formula:** $C_{20}H_{40}O$ **Molecular Weight:** 296.53 g/mol **RIFM Number:** 924 **Stereochemistry:** One stereocenter and 2 possible stereoisomers	**CAS Registry Number:** 7541-49-3 **Synonyms:** 3,7,11,15-Tetramethyl-2-hexadecen-1-ol **Molecular Formula:** $C_{20}H_{40}O$ **Molecular Weight:** 296.53 g/mol **RIFM Number:** 6297 **Stereochemistry:** One stereocenter and 2 possible stereoisomers

2. Physical data*

1. **Boiling Point:** 202 °C (Fragrance Materials Association [FMA]), 132 °C (Private communication to FEMA), 357.29 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; closed cup (FMA)
3. **Log K_{OW}:** 8.32 (EPI Suite)
4. **Melting Point**: 48.14 °C (EPI Suite)
5. **Water Solubility:** 0.00327 mg/L (EPI Suite)
6. **Specific Gravity:** 0.850 (FMA), 0.847–0.858 (Private communication to FEMA)
7. **Vapor Pressure:** 0.00000163 mm Hg at 20 °C (EPI Suite v4.0), 3.22e-006 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless to pale yellow liquid with a floral, woody, balsamic odor

*All physical data is identical for both materials in the assessment.

3. Volume of use (worldwide band)

1 0.1–1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient* (Creme RIFM aggregate exposure model v3.2.6)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.015% (RIFM, 2021)
2. **Inhalation Exposure**:** 0.000030 mg/kg/day or 0.0020 mg/day (RIFM, 2021)
3. **Total Systemic Exposure***:** 0.00087 mg/kg/day (RIFM, 2021)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrance, inhalation exposure, and total exposure.

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:

a. **Genotoxicity:** Farnesol (CAS # 4602-84-0); geraniol (CAS # 106-24-1)
b. **Repeated Dose Toxicity:** Farnesol (CAS # 4602-84-0)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Farnesol (CAS # 4602-84-0)

e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References:
None.

8. Natural occurrence

Phytol is reported to occur in the following foods by the VCF*.

Acerola (Malpighia)	Grape brandy
Brown algae	Guava and feyoa
Cheddar cheese	Lamb and mutton
Cinnamomum species	Mentha oils
Curry (Bergera koenigii L.)	Milk and milk products

2-Hexadecen-1-ol, 3,7,11,15-tetramethyl- is not reported to occur in food by the VCF.

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

9. REACH dossier

Available for phytol and 2-hexadecen-1-ol, 3,7,11,15-tetramethyl-; accessed 03/03/22.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for phytol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.21
2	Products applied to the axillae	0.062
3	Products applied to the face/body using fingertips	1.2
4	Products related to fine fragrances	1.2
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.29
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.29
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.29
5D	Baby cream, oil, talc	0.097
6	Products with oral and lip exposure	0.68
7	Products applied to the hair with some hand contact	2.0
8	Products with significant ano-genital exposure (tampon)	0.097
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.3
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.0020
10B	Aerosol air freshener	8.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.097
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note.
[a] Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For phytol, the basis was the reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 10%, and a skin sensitization NESIL of 2700 μg/cm^2.
[b] For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c] Calculations by Creme RIFM Aggregate Exposure Model v3.2.6.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, phytol does not present a concern for genotoxicity.

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

There are no data assessing the mutagenic activity of phytol; however, read-across can be made to farnesol (CAS # 4602-84-0; see Section VI). The mutagenic activity of farnesol 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 TA102 were treated with farnesol 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 concentration in the presence or absence of S9 (RIFM, 2008). Under the conditions of the study, farnesol was not mutagenic in the Ames test, and this can be extended to phytol.

There are no data assessing the clastogenic activity of phytol; however, read-across can be made to geraniol (CAS # 106-24-1; see Section VI). The clastogenic activity of geraniol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in DMSO/corn oil via the oral route to groups of male NMRI mice. Doses of 375, 750, or 1500 mg/kg were administered. Mice from each dose level were euthanized at 24 and 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2010). Under the conditions of the study, geraniol was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to phytol.

Based on the data available, read-across materials farnesol and

geraniol do not present a concern for genotoxic potential, and this can be extended to phytol.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated toxicity data on phytol. Read-across material farnesol (CAS # 4602-84-0; see Section VI) has sufficient repeated dose toxicity data that can be used to support the repeated dose toxicity endpoint. A gavage 28-day subchronic toxicity study was conducted in a group of 20 CD rats/sex/group rats 0 (corn oil), 500, or 1000 mg/kg/day farnesol. Ten rats from each group were maintained for an additional period of 28 days for a treatment-free recovery period. No treatment-related mortality was observed during the study, and farnesol had no significant effects on body weight, food consumption, clinical signs, or hematology/coagulation parameters. Modest but statistically significant alterations in several clinical chemistry parameters were observed at the termination of farnesol exposure; all clinical pathology effects were reversed during the recovery period. At the termination of dosing, the activities of CYP1A, CYP2A1-3, CYP2B1/2, CYP2C11/12, CYP2E1, CYP3A1/2, CYP4A1-3, CYP19, glutathione reductase, NADPH/quinone oxidoreductase, and UDP-glucuronosy ltransferase were significantly increased in the livers of farnesol-treated rats; farnesol also increased the activity of glutathione S-transferase in the kidney. The effects of farnesol on hepatic and renal enzymes were reversed during the recovery period. At the end of the dosing period, increases in absolute and relative liver and kidney weights were seen in farnesol-treated rats. These increases may be secondary to the induction of drug-metabolizing enzymes since organ weight increases were not associated with histopathologic alterations and were reversed upon discontinuation of farnesol exposure. Administration of farnesol at doses of up to 1000 mg/kg/day induced reversible increases in the activities of several hepatic and renal drug-metabolizing enzymes in rats while inducing only minimal toxicity. The NOAEL was determined to be 1000 mg/kg/day, the highest dose tested, since no treatment-related adverse effects were reported (Horn et al., 2005).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3, or 333 mg/kg/day.

Therefore, the phytol MOE for the repeated dose toxicity endpoint can be calculated by dividing the farnesol NOAEL in mg/kg/day by the total systemic exposure for phytol, 333/0.00087 or 382758.

In addition, the total systemic exposure to phytol (0.87 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic reference dose (RfD) of 3.33 mg/kg/day.

11.1.3. Derivation of subchronic RfD

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for Phytol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/14/21.

11.1.4. Reproductive toxicity

There are insufficient reproductive toxicity data on phytol or any read-across materials. The total systemic exposure to phytol is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.4.1. Risk assessment. There are no reproductive toxicity data on phytol or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to phytol (0.87 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/14/21.

11.1.5. Skin sensitization

Based on the existing data and read-across material farnesol (CAS # 4602-84-0), phytol is considered a skin sensitizer with a defined NESIL of 2700 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

11.1.5.1. Risk assessment. Insufficient skin sensitization studies are available for phytol. Based on the existing data and read-across material farnesol (CAS # 4602-84-0; see Section VI), phytol is considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0). The read-across material farnesol was found to be negative in the *in vitro* direct peptide reactivity assay (DPRA) (RIFM, 2015b). However, in KeratinoSens, h-CLAT, and U937-CD86 tests, farnesol was found to be positive (RIFM, 2015a; Urbisch, 2015; Piroird et al., 2015). In multiple murine local lymph node assays (LLNAs), farnesol was found to be sensitizing with a weighted mean EC3 value of 4.8% (1200 μg/cm^2) (RIFM, 2004a; RIFM, 2004b). In a human maximization study, phytol was found to be sensitizing (RIFM, 1977b). The read-across material, farnesol, was found to be sensitizing in some human maximization tests, while it was not shown to be sensitizing in other human maximization tests (RIFM, 1977a; RIFM, 1978; RIFM, 1977b; RIFM, 1974; RIFM, 1976; RIFM, 1975). Additionally, in Confirmation of No Induction in Humans test (CNIH) with 15% (8267 μg/cm^2) of farnesol in 1:3 ethanol: diethyl phthalate (EtOH:DEP), a reaction indicative of sensitization was observed in 1/107 volunteers, but it did not reoccur at rechallenge (RIFM, 2013b; RIFM, 2013c). In another CNIH with 5% (2755 μg/cm^2) of farnesol in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 108 volunteers (RIFM, 2004c).

Based on the weight of evidence (WoE) from structural analysis, human studies, and read-across to farnesol, phytol is a sensitizer with a WoE NESIL of 2700 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products based on skin

Table 1
Data summary for farnesol as read-across material for phytol.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μgcm^2	WoE NESIL[c] μg/cm^2
1200 [2]	oderate	2755	NA	6900	2700

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 3.33 mg/kg/day.

Additional References: Klecak (1985); RIFM, 2004d; RIFM, 1983; RIFM, 1995; Hausen et al., 1992; Hausen et al., 1995; Ishihara et al., 1986; Wantanabe, 1985; ECHA, 2017b.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.6. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, phytol would not be expected to present a concern for photoirritation or photoallergenicity.

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

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/24/21.

11.1.7. Local Respiratory Toxicity

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

11.1.7.1. Risk assessment. There are insufficient inhalation data available on phytol. Based on the Creme RIFM Model, the inhalation exposure is 0.0020 mg/day. This exposure is 700 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: Tsuchiya et al., 1992.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.2. 2. environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of phytol 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, phytol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify phytol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017b). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current VoU (2019), phytol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. Biodegradation:

For CAS # 150-86-7.

RIFM, 2011: A study was conducted following OECD TG 301F. 30 mg/L of the test material was incubated for a period of 62 days. The test material underwent 78% biodegradation after 62 days (73% after 28 days). The 10-day window criterion was fulfilled.

Ecotoxicity:

No data available.

11.2.1.3. Other available data. Phytol has been registered under REACH, and the following additional data is available (ECHA, 2017c):

An acute fish (*Danio rerio*) toxicity test was conducted according to the EU method C.1 under static conditions. The 96-h LC50 value based on nominal test concentration was reported to be > 100 mg/L.

A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h LC50 value based on nominal test concentration was reported to be > 100 mg/L.

A *Daphnia magna* reproduction test was conducted according to the OECD 211 guideline under flow-through conditions. The 21-day NOEC value based on the initial measured concentration was reported to be ≥ 55.7 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 and NOEC value based on the mean measured concentration for growth rate was reported to be > 1.34 mg/L.

A ready biodegradability of the test material (CAS # 7541-49-3) was evaluated using the CO_2 evolution test according to the OECD 301B guideline. Biodegradation of 76.5% was observed after 28 days.

11.2.1.4. 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.00127			1000000	0.0000013	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.651	0.153	0.009			Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.000514	0.000524	0.004	10000	0.000051	Neutral Organic
***Tier 3: Measured Data (including REACH)**						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	>100					
Daphnia		>100	55.7			
Algae		1.34	1.34	50	26.8	

*The Tier 3: Measured Data are from isophytol

Framework: Salvito et al., 2002).

Exposure	Europe	North America
Log K_{ow} Used	8.32	8.32
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band*	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional VoU.

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

The RIFM PNEC is 26.8 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 08/10/22.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

Search keywords: CAS number and/or material names.

Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 08/10/22.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.114270.

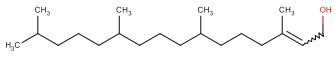
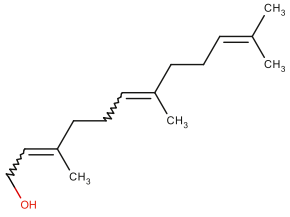
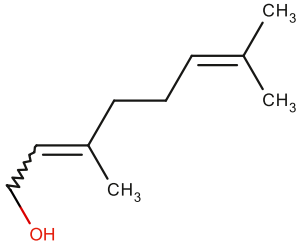
Appendix

Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Phytol	Farnesol	Geraniol
CAS No.	150-86-7	4602-84-0	106-24-1
Structure			
Similarity (Tanimoto Score)		0.39	0.41
Endpoint		• Genotoxicity • Skin sensitization • Repeated dose toxicity	• Genotoxicity
Molecular Formula	$C_{20}H_{40}O$	$C_{15}H_{26}O$	$C_{10}H_{18}O$
Molecular Weight (g/mol)	296.54	222.37	154.25
Melting Point (°C, EPI Suite)	48.14	3.24	−10.78
Boiling Point (°C, EPI Suite)	357.29	319.11	225.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.00	0.01	4.00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.00	1.29	531.00
Log K_{OW}	8.32	5.77	3.47
J_{max} (μg/cm^2/h, SAM)	0.00	0.21	64.26
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	97.78	25.53	1.17
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	No alert found
Oncologic Classification	Not classified	Not classified	Not classified
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized	Not categorized	
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found	No alert found	
Protein Binding (OECD)	No alert found	No alert found	
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.	Alert for Schiff base formation identified.	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on phytol (CAS # 150-86-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, farnesol (CAS # 4602-84-0) and geraniol (CAS # 106-24-1) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Farnesol (CAS # 4602-84-0) was used as a read-across analog for the target material, phytol (CAS # 150-86-7), for the skin sensitization, genotoxicity, and repeated dose toxicity endpoints.
  - o The target material and the read-across analog belong to a class of α, β-unsaturated primary alcohols.
  - o The key difference between the target material and the read-across analog is that the target material has 20 carbons with one vinylene bond, whereas the read-across analog has 15 carbons with 3 vinylene bonds. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto scores. Differences between the structures that affect the Tanimotos score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$10%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$40%. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and the read-across analog have an alert for Schiff base formation for the Toxtree Skin Sensitization Reactivity Domains. This alert is due to the β-substituted α,β-unsaturated primary alcohol functionality in both compounds. Data reported in the skin sensitization section shows that both target material and read-across analog are weak sensitizers. Therefore, data are consistent with *in silico* alerts.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Geraniol (CAS # 106-24-1) was used as a read-across analog for the target material, phytol (CAS # 150-86-7), for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of α, β-unsaturated primary alcohols.
  - o The key difference between the target material and the read-across analog is that the target material has 20 carbons with 1 vinylene bond, whereas the read-across analog has 10 carbons with 2 vinylene bonds. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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