Food and Chemical Toxicology 183 (2024) 114396

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 2,6,10-trimethylundeca-5,9-dienol, CAS Registry Number 24048-14-4

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ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

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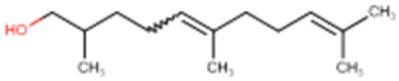
https://doi.org/10.1016/j.fct.2023.114396
Received 17 August 2022; Received in revised form 12 December 2023; Accepted 14 December 2023
Available online 21 December 2023

Version: 081722. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: 2,6,10-Trimethylundeca-5,9-dienol
CAS Registry Number: 24048-14-4

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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.

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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.

2,6,10-Trimethylundeca-5,9-dienol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog farnesol (CAS # 4602-84-0) show that 2,6,10-trimethylundeca-5,9-dienol is not expected to be genotoxic and provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on analogs geraniol (CAS # 106-24-1) and nerol (CAS # 106-25-2) provide a calculated MOE >100 for the reproductive toxicity endpoint. Target data and data from analog farnesol (CAS # 4602-84-0) provided 2,6,10-trimethylundeca-5,9-dienol a NESIL of 2700 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on UV spectra; 2,6,10-trimethylundeca-5,9-dienol is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material; the exposure to 2,6,10-trimethylundeca-5,9-dienol is below the TTC (1.4 mg/day). For the hazard assessment based on the screening data, 2,6,10-trimethylundeca-5,9-dienol is not PBT as per the IFRA Environmental Standards. For the risk assessment, 2,6,10-trimethylundeca-5,9-dienol was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2008a; RIFM, 2008b; Rupa et al., 2003)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(Horn et al., 2005)
Reproductive Toxicity: Developmental toxicity NOAEL = 191.2 mg/kg/day. Fertility NOAEL = 1000 mg/kg/day.	(ECHA REACH Dossier: Nerol; ECHA, 2013; RIFM, 2010)
Skin Sensitization: NESIL = 2700 μg/cm^2.	(RIFM, 2004c)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.	(UV Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.89 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 1600 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 0.339 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: 0.339 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.000339 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 2,6,10-Trimethylundeca-5,9-dienol
2. **CAS Registry Number:** 24048-14-4
3. **Synonyms:** Dihydroapofarnesol; 5,9-Undecadien-1-ol, 2,6,10-trimethyl-; 2,6,10-Trimethylundeca-5,9-dien-1-ol; Profarnesol; 2,6,10-Trimethylundeca-5,9-dienol
4. **Molecular Formula:** $C_{14}H_{26}O$
5. **Molecular Weight:** 210.36 g/mol
6. **RIFM Number:** 5474
7. **Stereochemistry:** Isomer not specified. Two geometric centers and 4 possible isomers.

2. Physical data

1. **Boiling Point:** 295.85 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 5.36 (EPI Suite)
4. **Melting Point**: 20.6 °C (EPI Suite)
5. **Water Solubility:** 3.306 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000968 mm Hg at 20 °C (EPI Suite v4.0), 0.000176 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L • mol-1 • cm-1)
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1 . <0.1 metric ton per year (IFRA, 2019).

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1 . **95**th **Percentile Concentration in Fine Fragrance:** 0.029% (RIFM, 2020).
2 . **Inhalation Exposure*:** 0.000012 mg/kg/day or 0.0011 mg/day (RIFM, 2020).
3 . **Total Systemic Exposure**:** 0.000040 mg/kg/day (RIFM, 2020).

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford, 2015; Safford e al., 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%. As a conservative approach, we are assuming that 100% of the material exposed via the skin is bioavailable, thereby deriving the most stringent MOE. Since the MOE is > 100 (see the repeated dose and reproductive toxicity sections), we then refined the exposure using an *in silico* Skin Absorption Model (SAM) to determine the Maximum Allowable Concentrations for each category listed in Section X.
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)
b. **Repeated Dose Toxicity:** Farnesol (CAS # 4602-84-0)
c. **Reproductive Toxicity:** Geraniol (CAS # 106-24-1) and nerol (CAS # 106-25-2)
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

2,6,10-Trimethylundeca-5,9-dienol is not reported to occur in foods 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.

9. REACH Dossier

2,6,10-Trimethylundeca-5,9-dienol has been pre-registered for 2010; no dossier available as of 03/03/22.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2,6,10-trimethylundeca-5,9-dienol 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

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
7	Products applied to the hair with some hand contact	2.4
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)	8.1
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 2,6,10-trimethylundeca-5,9-dienol, the basis was the reference dose of 1.9 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 2700 μg/cm^2.

bFor 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).

cCalculations 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 and use levels, 2,6,10-trimethylundeca-5,9-dienol does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. 2,6,10-Trimethylundeca-5,9-dienol was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays 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 and clastogenic activity of 2,6,10-trimethylundeca-5,9-dienol; 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, 2008a). Under the conditions of the study, farnesol was not mutagenic in the Ames test, and this can be extended to 2,6,10-trimethylundeca-5,9-dienol.

The clastogenicity of farnesol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with farnesol in DMSO at concentrations up to 2270 μg/mL in a dose range finding study; the main study was conducted at concentrations up to 242 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (RIFM, 2008b). Under the conditions of the study, farnesol was considered to be non-clasctogenic in the *in vitro* chromosome aberration assay, and this can be extended to 2,6,10-trimethylundeca-5,9-dienol.

Based on the available data, farnesol does not present a concern for genotoxic potential, and this can be extended to 2,6,10-trimethylundeca-5,9-dienol.

Additional References: Florin (1980); RIFM, 1989; Rupa (2003); RIFM, 2008c.

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

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for 2,6,10-trimethylundeca-5,9-dienol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2,6,10-trimethylundeca-5,9-dienol. 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. 10 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-glucuronosyltransferase 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 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 2,6,10-trimethylundeca-5,9-dienol 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 2,6,10-trimethylundeca-5,9-dienol, 333/0.00004, or 25000000.

In addition, the total systemic exposure for 2,6,10-trimethylundeca-5,9-dienol (0.040 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None
Literature Search and Risk Assessment Completed On: 10/14/21

11.1.3. Reproductive toxicity

The MOE for 2,6,10-trimethylundeca-5,9-dienol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2,6,10-trimethylundeca-5,9-dienol. There are several reproductive toxicity studies on read-across analogs geraniol (CAS # 106-24-1; see Section VI) and nerol (CAS # 106-25-2; see Section VI) that can be used for the reproductive toxicity endpoint.

An OECD 414/GLP prenatal developmental toxicity study was conducted on female Wistar rats. Groups of 25 time-mated rats/dose were administered geraniol 60 (a mixture of geraniol [a stereoisomer, CAS # 106-24-1; see Section VI] and nerol, approximately 60:40) via gavage at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil on gestation days (GDs) 6–19. A treatment-related decrease in food consumption was reported among animals of the high-dose group. There was a significant decrease in bodyweight gain (14% below the control) among dams of the high-dose group. The bodyweight gain among dams of the mid-dose group also was significantly decreased (13% below the control), indicating systemic toxicity due to treatment administration. High-dose group fetal weights were statistically significantly reduced (8% below the control) as compared to the controls. This slight reduction was considered to be subsequent to the lower bodyweight gain among the dams of the high-dose group. Fetal examination revealed no effect of treatment administration on the morphological structures up to the highest dose tested. Incidences of a dilated renal pelvis and incomplete ossification of various skeletal elements represented temporary delays in development, which have no permanent effect on the morphology and function of the affected organs or structures. The NOAEL for prenatal developmental toxicity was considered to be 300 mg/kg/day, based on a decrease in fetal weights among high-dose group fetuses and incidences of the dilated renal pelvis and incomplete skeletal ossifications secondary to maternal toxicity among high-dose group animals (RIFM, 2015c).

An OECD 422 dietary combined repeated dose with a reproduction/developmental toxicity screening test was conducted in Han Wistar rats. Nerol was administered by dietary admixture (initially mixed with 2% corn oil to avoid evaporation) to 3 groups of rats for up to 42 consecutive days for main-phase males, toxicity females, and recovery animals, between 41 and 53 days (including the 3-week exposure phase, pairing, gestation, and early lactation) for main-phase females. The dietary concentrations of 0, 3000, 6000, and 12000 ppm were equivalent to the mean achieved doses of 0, 191.2, 374, and 720 mg/kg/day, respectively. Each dose group was subdivided into the following phases: main phase (males: 10 animals/dose for 3000 and 6000 ppm dose groups; 5 males/dose for 0 and 12000 ppm; females: 10 animals/dose for control and all dose groups) and toxicity phase (5 female/dose). Two recovery groups (5 rats/sex/dose) were treated with 0 or 12000 ppm for 42 consecutive days and then maintained without treatment for a further 14 days. The control group was treated with a basal laboratory diet. In addition to systemic toxicity parameters, the reproductive toxicity parameters were also assessed. Maternal toxicity was evident by the decrease in the overall bodyweight gain among females treated at 12000 ppm. During the pre-pairing period, females showed a decrease in bodyweight gain, especially during the first week of the treatment. From day 8 to the end of the study, 12000 ppm toxicity group females showed a 25% decrease in mean bodyweight gain compared to controls. During the recovery phase, their mean bodyweight gain was 3 times higher than the concurrent control group. During the gestation period, main-phase females showed an overall decrease in mean bodyweight gain at 3000, 6000, and 12000 ppm, mainly observed during the last week of gestation. A reduction in food intake was maintained at the high-dose throughout the treatment period in both males and females but particularly for main-phase females, reflecting its low palatability. During the lactation period, the dietary intake of the main-phase females was reduced in all treatment groups. A significant dose-related increase in post-implantation loss was observed with the mean values outside the historical control data at the mid- and high-doses. This change was considered to be treatment-related. The LOAEL for maternal toxicity was considered to be 3000 ppm or 191.2 mg/kg/day, based on decreased bodyweight gain during the last week of gestation. The NOAEL for fertility was considered to be 12000 ppm or 720 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity was considered to be 3000 ppm or 191.2 mg/kg/day, based on increased post-implantation loss (ECHA, 2013).

In an OECD 421 study, geraniol 60 (mixture of geraniol [stereoisomer, CAS # 106-24-1; see Section VI] and nerol, approximately 60:40) was administered to groups of 10 Wistar rats/sex/dose at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil. Rats were gavaged daily for 2 weeks plus a mating period (2 weeks maximum), a post-mating period of 1 week (males only), through gestation, and 4 days postpartum for females. Males were euthanized after a minimum of 28 days, and females were euthanized after a minimum of 4 days postpartum. There were no alterations in the mating and fertility indices among treated animals as compared to the controls. The duration of gestation and gestation index were comparable to the female controls. There were no treatment-related alterations in the male and female reproductive organs up to the highest dose tested. The NOAEL for male and female fertility was considered to be 1000 mg/kg/day. At 1000 mg/kg/day, the number of live-born pups was statistically significantly decreased in high-dose females, resulting from a lower number of pups delivered and a higher number of stillborn pups. The viability index indicating pup mortality during early lactation (postnatal days 0–4) was distinctly reduced (−25%) in the high-dose group, resulting from significantly higher numbers of dead (7 vs. 0 in control) and cannibalized pups (11 vs. 0 in control). In the mid-dose group, the viability index was reduced (91% of controls), resulting from a higher number of dead pups (5 vs. 0 in control) and a significantly higher number of cannibalized pups (6 vs. 0 in control). The pups from 1000 mg/kg/day dams were not properly nursed, resulting in a decreased viability index and a statistically significant reduction in body weights. At 300 mg/kg/day, the number of stillborn pups was slightly increased (5.6% vs. 0.0%–4.5% in historical control data), and some pups were not properly nursed due to insufficient maternal care, resulting in a reduced viability index. Increased incidences (5% and 10%) of an empty stomach were observed in the mid- and high-dose group pups, respectively. The increased total number of stillborn pups in the high-dose group was only influenced by one dam's litter. The NOAEL for developmental toxicity was considered to be 100 mg/kg/day, based on a decrease in viability index and an increase in stillborn pups among higher dose group animals (RIFM, 2010).

A NOAEL of 191.2 mg/kg/day from the OECD 422 study on the read-across material nerol, which was considered to be the more relevant study, was selected for the developmental toxicity endpoint. **Therefore, the 2,6,10-trimethylundeca-5,9-dienol MOE for the developmental toxicity endpoint can be calculated by dividing the nerol NOAEL in mg/kg/day by the total systemic exposure to 2,6,10-trimethylundeca-5,9-dienol, 191.2/0.00004, or 4780000.**

Since the fertility NOAEL was considered to be the highest tested dose for both OECD 422 and OECD 421 studies, 1000 mg/kg/day was selected as the fertility NOAEL from the OECD 421 study conducted on the geraniol/nerol mixture. **Therefore, the 2,6,10-trimethylundeca-5,9-dienol MOE for the fertility endpoint can be calculated by dividing the nerol NOAEL in mg/kg/day by the total systemic exposure to 2,6,10-trimethylundeca-5,9-dienol, 1000/0.00004, or 25000000.**

In addition, the total systemic exposure to 2,6,10-trimethylundeca-5,9-dienol (0.04 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 materials 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. (RIFM, 2020a) and a reference dose (RfD) of 1.9 mg/kg/day.

11.1.3.1.1. Derivation of 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 RfD for 2,6,10-trimethylundeca-5,9-dienol was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 191.2 mg/kg/day by the uncertainty factor, 100 = 1.9 mg/kg/day.

Additional References: None

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

11.1.4. Skin sensitization

Based on the available data and read-across to farnesol (CAS # 4602-84-0), 2,6,10-trimethylundeca-5,9-dienol is considered a skin sensitizer with a defined NESIL of 2700 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 2,6,10-trimethylundeca-5,9-dienol. Based on the existing data and read-across material farnesol (CAS # 4602-84-0; see Section VI), 2,6,10-trimethylundeca-5,9-dienol is considered a skin sensitizer. The chemical structure of farnesol indicates that it would be expected to react with skin proteins directly, while the target material is not expected to react with skin proteins (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). The read-across material farnesol was found to be both sensitizing and non-sensitizing in several human maximization tests (RIFM, 1977a; RIFM, 1978; RIFM, 1977b; RIFM, 1974; RIFM, 1976; RIFM, 1975). In 2 Confirmation of No Induction in Humans tests (CNIHs) with 5% or 1550 μg/cm^2 read-across farnesol in petrolatum, no reactions indicative of sensitization were observed in any of the 103 and 101 volunteers, respectively (RIFM, 2000a; RIFM, 2000b). Similarly, in 2 other CNIHs with 15% or 8267 μg/cm^2 read-across farnesol in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 107 volunteers, respectively (RIFM, 2013a; RIFM, 2013c). Additionally, in a CNIH with 5% or 2756 μg/cm^2 read-across farnesol in 1:3 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 108 volunteers (RIFM, 2004c).

Based on the available data on read-across material farnesol, summarized in Table 1, 2,6,10-trimethylundeca-5,9-dienol is considered a skin sensitizer with a defined NESIL of 2700 μg/cm^2. Section X provides the maximum acceptable concentrations in finished products based on the application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020a) and an RfD of 1.9 mg/kg/day.

Additional References: RIFM, 1970; RIFM, 2004d; Klecak (1985); RIFM, 2004e; RIFM, 1983; RIFM, 1995; Hausen et al., 1992, Hausen et al., 1995; Ishihara et al., 1986; Wantanabe, 1985.

Literature Search and Risk Assessment Completed On: 10/13/21

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) μg/cm^2	WoE NESIL[3] μg/cm^2
1200 [2]	Moderate	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.

11.1.5. Photoirritation/photoallergenicity

Based on UV absorption spectra, 2,6,10-trimethylundeca-5,9-dienol would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for 2,6,10-trimethylundeca-5,9-dienol experimental models. UV absorption spectra indicate no significant absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2,6,10-trimethylundeca-5,9-dienol does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. The available UV absorption spectrum for 2,6,10-trimethylundeca-5,9-dienol demonstrates that this material does not absorb in the region of 290–400 nm. The molar absorption coefficient is well below the benchmark (1000 L mol^{-1} • cm^{-1}) of concern for photoirritating effects (Henry et al., 2009).

Additional References: None

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

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2,6,10-trimethylundeca-5,9-dienol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2,6,10-trimethylundeca-5,9-dienol. Based on the Creme RIFM Model, the inhalation exposure is 0.0011 mg/day. This exposure is 1272.7 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: 10/15/21

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,6,10-trimethylundeca-5,9-dienol 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)(mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.339			1000000	0.000339	

Framework, 2,6,10-trimethylundeca-5,9-dienol 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 2,6,10-trimethylundeca-5,9-dienol as possibly persistent but did identify 2,6,10-trimethylundeca-5,9-dienol as possibly 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, 2017a). 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).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2019), 2,6,10-trimethylundeca-5,9-dienol does present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. 2,6,10-Trimethylundeca-5,9-dienol has been pre-registered for REACH with no additional data at this time.

11.2.1.3. 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 Framework: Salvito et al, 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.36	5.36
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 additional assessment is necessary.

The RIFM PNEC is 0.000339 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

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.

CRediT authorship contribution statement

G. Sullivan: Writing – review & editing.

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.2023.114396.

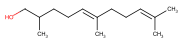
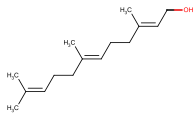
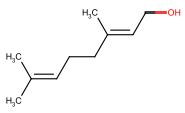
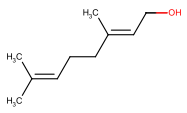
Appendix

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, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (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.

Principal Name	Target Material	Read-across Material	Read-across Material	Read-across Material
	2,6,10-Trimethylundeca-5,9-dienol	Farnesol	Geraniol	Nerol
CAS No.	24048-14-4	4602-84-0	106-24-1	106-25-2
Structure				
Similarity (Tanimoto Score)		0.68	0.58	0.58
Read-across Endpoint		• Genotoxicity • Repeated Dose Toxicity • Skin Sensitization	• Reproductive toxicity	• Reproductive toxicity
Molecular Formula	$C_{14}H_{26}O$	$C_{15}H_{26}O$	$C_{10}H_{18}O$	$C_{10}H_{18}O$
Molecular Weight (g/mol)	210.36	222.37	154.25	154.25
Melting Point (°C, EPI Suite)	20.60	3.24	−10.78	−10.78
Boiling Point (°C, EPI Suite)	295.85	319.11	225.00	225.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.02346	0.00525	4.00	4.00
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.36	5.77	3.47	3.47
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.306	1.287	531.00	531.00
J_{max} (μg/cm^2/h, SAM)	6.022	3.411	64.258	64.258
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.85E+01	2.55E+01	1.16E+00	1.16E+00
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found		
Carcinogenicity (ISS)	• Structural alert for nongenotoxic carcinogenicity|Substituted n-alkylcarboxylic acids (Nongenotox)	• No alert found		

(*continued on next page*)

(*continued*)

Principal Name	Target Material	Read-across Material	Read-across Material	Read-across Material
	2,6,10-Trimethylundeca-5,9-dienol	Farnesol	Geraniol	Nerol
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	• Not classified	• Not classified		
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized	• Not categorized		
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure		• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)		• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
Skin Sensitization				
Protein Binding (OASIS v1.1)	• No alert found	• No alert found		
Protein Binding (OECD)	• No alert found	• No alert found		
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)		
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found		
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• Alert for Schiff base formation		
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	See Supplemental Data 4

Summary

There are insufficient toxicity data on 2,6,10-trimethylundeca-5,9-dienol (CAS # 24048-14-4). 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), geraniol (CAS # 106-24-1), and nerol (CAS # 106-25-2) 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, 2,6,10-trimethylundeca-5,9-dienol (CAS # 24048-14-4), for the genotoxicity, skin sensitization, and repeated dose toxicity endpoints.
  - o The target material and the read-across analog belong to a class of unsaturated primary alcohols.
  - o The target material and the read-across analog share a primary alcohol group within an unsaturated branched alkene chain with a terminal isobutylene group.
  - o The key difference between the target material and the read-across analog is that the target material has 14 carbons with 2 double bonds, whereas the read-across analog has 15 carbons and is an α, β-unsaturated primary alcohol with 3 double bonds. This structural difference makes the read-across analog more reactive from a toxicological point of view.
  - o 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 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 presents a carcinogenicity alert for substituted n-alkylcarboxylic acids, which is not found for the read-across analog. This alert is due to the methyl β-substitution. Substances belonging to this chemical class are potentially reactive as peroxisome proliferators (PPs). PPs are a diverse group of chemicals, including hypolipidemic drugs, plasticizers, and herbicides, that were found to cause liver cancer when chronically administered to rats and mice. These chemicals are considered nongenotoxic agents, given generally negative results in genotoxicity assays. Even if the mechanism by which these chemicals cause tumors is not fully understood, peroxisome proliferator-activated receptor α (PPAR-α) is thought to mediate most of the PP effects in the rodent liver. The data described in the genotoxicity section show that the MOE is adequate at the current level of use. The predictions are therefore superseded by the data.
  - o The read-across material has an alert for Schiff base formation for Skin Sensitization Reactivity Domains because farnesol is an α, β-unsaturated primary alcohol. The data described in the skin sensitization section shows that farnesol is a weak skin sensitizer. Data are consistent with the *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, 2,6,10-trimethylundeca-5,9-dienol (CAS # 24048-14-4), for the reproductive toxicity endpoint.
  - o The target material and the read-across analog belong to a class of unsaturated primary alcohols.

- The target material and the read-across analog share a primary alcohol group within an unsaturated branched alkene chain with a terminal isobutylene group.
- The key difference between the target material and the read-across analog is that the target material has 14 carbons with 2 double bonds, whereas the read-across analog has 10 carbons and is an α, β-unsaturated primary alcohol with 2 double bonds. This structural difference is toxicologically insignificant.
- 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.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- 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$80%. 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.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog do not have toxicity alerts. Data are consistent with the *in silico* alerts.
- The target material 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.

- Nerol (CAS # 106-25-2) was used as a read-across analog for the target material, 2,6,10-trimethylundeca-5,9-dienol (CAS # 24048-14-4), for reproductive toxicity endpoint.
  - The target material and the read-across analog belong to a class of unsaturated primary alcohols.
  - The target material and the read-across analog share a primary alcohol group within an unsaturated branched alkene chain with a terminal isobutylene group.
  - The key difference between the target material and the read-across analog is that the target material has 14 carbons with 2 double bonds, whereas the read-across analog has 10 carbons and is an α, β-unsaturated primary alcohol with 2 double bonds. This structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - 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$80%. 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.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material 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.

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