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Short review

RIFM fragrance ingredient safety assessment, farnesal, CAS Registry Number 19317-11-4

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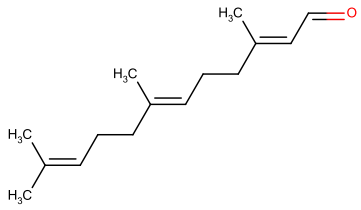

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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 Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
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, 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).

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*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.

Farnesal was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across-analog citral (CAS # 5392-40-5) show that farnesal is not expected to be genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose and developmental and reproductive toxicity endpoints. Read-across analog citral (CAS # 5392-40-5) provided farnesal a No Expected Sensitization Induction Level (NESIL) of 1400 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet (UV) spectra; farnesal is not phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to farnesal is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; farnesal was found not to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	NTP (2003)
Repeated Dose Toxicity: NOAEL = 20 mg/kg/day.	Ress (2003)
Developmental and Reproductive Toxicity: Developmental Toxicity NOAEL = 60 mg/kg/day. Reproductive Toxicity NOAEL = 1000 mg/kg/day.	(RIFM, 2016a; MHW, 1996)
Skin Sensitization: NESIL = 1400 μg/cm^2.	RIFM (2008b)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV Spectra, RIFM Database; RIFM, 1985)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.73 (BIOWIN 3)	(EPI Suite v4.1; US EPA 2012a)
Bioaccumulation: Screening-level: 2855 L/kg	(EPI Suite v4.1; US EPA 2012a)
Ecotoxicity: Screening-level: LC50: 0.166 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: 0.166 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.000166 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America (no use reported) and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Farnesal
2. **CAS Registry Number:** 19317-11-4
3. **Synonyms:** 2,6,10-Dodecatrienal, 3,7,11-trimethyl-; 3,7,11-Trimethyl-2,6,10-dodecatrienal; 3,7,11-Trimethyl dodecatrien-2,6,10-al-1; 3,7,11-Trimethyldodeca-2,6,10-trienal; Farnesal
4. **Molecular Formula:** $C_{15}H_{24}O$
5. **Molecular Weight:** 220.35

6. **RIFM Number:** 6231

2. physical data

1. **Boiling Point:** 302.17 °C (EPI Suite)
2. **Flash Point:** > 212.00 °F; TCC (>100.00 °C)*
3. **Log K_{OW}:** 5.74 (EPI Suite)
4. **Melting Point**: 16.65 °C (EPI Suite)
5. **Water Solubility:** 0.4278 mg/L (EPI Suite)
6. **Specific Gravity:** 0.89000 to 0.90000 @ 25.00 °C*
7. **Vapor Pressure:** 0.00105 mm Hg @ 20 °C (EPI Suite v4.0), 0.00174 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A pale yellow to yellow clear liquid with a medium floral, minty odor*

* http://www.thegoodscentscompany.com/data/rw1044051.html#toorgano, retrieved 02/02/16.

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure

1. 95th **Percentile Concentration in Hydroalcoholics:** 0.0069% (RIFM, 2016b)

2. Inhalation Exposure*: 0.000039 mg/kg/day or 0.0030 mg/day (RIFM, 2016b)

3. Total Systemic Exposure:** 0.00010 mg/kg/day (RIFM, 2016b)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015, 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, 2015, 2017; Safford, 2015, 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 v2.6	OECD QSAR Toolbox v3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Citral (CAS # 5392-40-5)
   b. **Repeated Dose Toxicity:** Citral (CAS # 5392-40-5)
   c. **Developmental and Reproductive Toxicity:** Citral (CAS # 5392-40-5)
   d. **Skin Sensitization:** Citral (CAS # 5392-40-5)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

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

Farnesal is reported to occur in the following foods by the VCF*:

Cardamom (*Elettaria cardamomum* (L.) Maton)
Ginger (*Zingiber* species)
Tomato (*Lycopersicon esculentum* Mill.)

*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

Pre-registered for 2010; no dossier available as of 03/31/20.

10. Conclusion

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

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.11
2	Products applied to the axillae	0.032
3	Products applied to the face/body using fingertips	0.11
4	Products related to fine fragrances	0.60
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.15
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.15
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.15
5D	Baby cream, oil, talc	0.051
6	Products with oral and lip exposure	0.11
7	Products applied to the hair with some hand contact	0.34
8	Products with significant ano-genital exposure (tampon)	0.051
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.57
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.57
10B	Aerosol air freshener	4.2
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.051
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 farnesal, the basis was the reference dose of 0.6 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 1400 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).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, farnesal does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. Farnesal was assessed in the BlueScreen assay and found positive for both cytotoxicity and genotoxicity, with and without metabolic activation, indicating a potential concern for genotoxicity (RIFM, 2013a).

There are no studies assessing the mutagenic potential of farnesal. The mutagenic potential of the read-across material citral (CAS # 5392-40-5; see Section VI) was assessed in a GLP-compliant Ames assay conducted according to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with citral at concentrations ranging from 1 to 220 μg/plate in the presence and absence of metabolic activation (S9). There were no significant increases in revertant colonies in any of the strains (NTP, 2003). Under the conditions of the study, citral was considered negative for mutagenicity in the Ames test.

The clastogenic activity of read-across analog citral was assessed by the National Toxicology Program (NTP). In an *in vitro* sister chromatid exchange (SCE) assay (OECD TG 479), citral was shown to induce SCEs in Chinese hamster ovary cells with and without S9 mix at toxic doses. A subsequent *in vitro* chromosome aberration study (OECD TG 473) demonstrated no significant increase in chromosomal aberrations after exposure to citral with or without S9. To confirm these results, an *in vivo* micronucleus assay was conducted in accordance with OECD TG 474. Groups of male B6C3F1 mice were injected intraperitoneally 3 times at 24-h intervals with 250–1000 mg/kg of citral in corn oil. Animals were euthanized 24 h after the third injection, and the bone marrow was assessed. There were no increases in polychromatic erythrocytes in the treatment groups compared to controls (NTP, 2003). Under the conditions of the study, citral was considered negative in the *in vivo* micronucleus assay.

Based on the available data, citral does not present a concern for genotoxic potential, and this can be extended to farnesal.

Additional References: NTP, 2003; Ishidate (1984); Lutz (1982); Eder (1982); Yoo (1986); Zeiger (1987); Kuroda (1984); Carneiro (1997); Gomes-Carneiro (1998); Duerksen-Hughes (1999); Yoo (1986); Oda (1978); Lopez (2011); RIFM, 2013b.

Literature Search and Risk Assessment Completed On: 10/06/20.

11.1.2. Repeated dose toxicity

The MOE for farnesal 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 farnesal. Read-across material citral (CAS # 5392-40-5; see Section VI) has sufficient repeated dose toxicity data. An NTP-sponsored chronic dietary study was conducted in compliance with GLP on groups of 50 F344/N rats/sex/group. The animals were administered citral (microencapsulated) at concentrations of 1000, 2000, or 4000 ppm for 104–105 weeks. Additional groups of 50 male and 50 female rats received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). The concentrations are equivalent to approximately 50, 100, and 210 mg/kg/day. The NOAEL for treatment-related non-neoplastic effects was 100 mg/kg/day, based on decreased body weight among the animals in the high-dose group (Ress, 2003). In another GLP study, groups of 50 B6C3F1 mice/sex/group were fed diets containing citral at concentrations of 500, 1000, or 2000 ppm for 104–105 weeks. Additional groups of 50 male and 50 female mice received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). The concentrations are equivalent to approximately 60, 120, and 260 mg/kg/day. There were significant decreases in body weights among mid- and high-dose group male mice. Body weights were also significantly decreased among all treated females. The incidences of malignant lymphoma in females occurred with a positive trend. The incidence in 2000 ppm females was significantly greater than that in the vehicle control group but was within the historical ranges in controls (all routes). To further characterize the nature of the lymphomas in the vehicle control and exposed mice, all cases of lymphoma were sectioned and immunostained using CD-3 to identify T cells and CD-45R (B220 clone) to identify B cells. Immunostaining of the lymphomas did not reveal any differences in the origin of the lymphomas in the vehicle control and the treatment group animals. There was a positive trend in the incidences of hepatomas (hepatocellular adenoma or carcinoma) in females but of no statistical significance. Inflammation and ulceration of the oral mucosa among the 2000 ppm group males and all treated females, adrenal cortical focal hyperplasia in high-dose group males, nephropathy among high-dose group females, and minimal tubule mineralization among the 500 and 1000 ppm group females were also reported, but the relevance of these incidences to treatment with citral could not be confirmed. The NOAEL for treatment-related non-neoplastic effects among males was considered to be 60 mg/kg/day, and the LOAEL for non-neoplastic effects among females was considered to be 60 mg/kg/day, based on a decrease in body weight among the treated animals. A NOAEL of 20 mg/kg/day was derived by dividing the LOAEL of 60 mg/kg/day among female mice by an uncertainty factor of 3. The derived NOAEL was determined to be 20 mg/kg/day (Ress, 2003; data also available in NTP, 2003). The most conservative NOAEL for repeated dose toxicity was determined from a dietary 104- to 105-week carcinogenicity study in mice to be 20 mg/kg/day, based on reduced body weights.

Therefore, the farnesal MOE for the repeated dose toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to farnesal, 20/0.00010 or 200000.

In addition, the total systemic exposure to farnesal (0.10 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.2. Derivation of reference dose (RfD). 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, 2008a; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 0.6 mg/kg/day.

The RfD for farnesal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental Toxicity sections) of 20 mg/kg/day by the uncertainty factor, 35 = 0.6 mg/kg/day.

The RfD was derived based on the ECHA-REACH DNEL for citral for General Population - Hazard via oral route (ECHA, 2011).

Additional References: Jackson (1987); Dieter (1993); Hagan (1967); Bar (1967); Abramovici (1983); Sandbank (1988); Abramovici (1985); RIFM, 1958; Leach (1956); Shillinger (1950); Abramovici (1980); Toaff (1979); Howes (2002); Geldof (1992); Servadio (1986a); Servadio (1986b); Servadio (1987); Abramovici (1987); Scolnik (1994a); Scolnik (1994b); Engelstein (1996); Kessler (1998); Golomb

(2001); Diliberto (1988a); Diliberto (1990); Diliberto (1989); Diliberto (1988b); Ishida (1989); Boyer (1990); Phillips (1976); Barbier (1983).

Literature Search and Risk Assessment Completed On: 10/05/20.

11.1.3. Developmental and reproductive toxicity

The MOE for farnesal is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on farnesal. Read-across material citral (CAS # 5392-40-5; see Section VI) has sufficient developmental and reproductive toxicity data.

A gavage developmental toxicity study was conducted on groups of 20 Wistar rats. The pregnant animals were treated with citral at dose levels of 0 (corn oil), 60, 125, 250, 500, or 1000 mg/kg/day on gestation days (GDs) 6–15. The study was terminated on GD 21. Administration of citral induced whole-litter loss at doses that were deemed to be maternally toxic (125–1000 mg/kg/day), suggesting that treatment-induced prenatal loss was a maternally-mediated effect. No increase in visceral anomalies was found at any dose. The LOAEL for both maternal and developmental toxicity was determined to be 60 mg/kg/day, based on maternal body weights and increased ratio of resorptions per implantations at higher doses (Nogueira, 1995).

An OECD 421 gavage reproduction toxicity screening test was conducted in Crj:CD (SD) rats. Citral was administered to rats via gavage at dose levels of 0, 40, 200, and 1000 mg/kg/day in males for 46 days and in females for 39–50 days, including before and through the mating and gestation periods and until day 3 of lactation. Body weights of pups were reduced at 1000 mg/kg/day, though there was no effect on viability or morphogenesis. The NOAEL for developmental toxicity was determined to be 200 mg/kg/day, due to decreased body weights among the high-dose group pups (MHW, 1996).

A reproductive toxicity screening study was conducted on 30 female Sprague Dawley rats/group, which were administered citral via gavage at dose levels of 0 (corn oil), 50, 160, and 500 mg/kg/day for 2 weeks prior to mating through GD 20. Subsequently, the effects of citral on the development of the offspring in utero and through lactation were also reported. There was no gross external alteration attributed to the test material in the fetuses up to the highest dose tested. However, there was a significant decrease in the average pup body weight at birth among the high-dose group animals as compared to controls. The NOAEL for the developmental toxicity was determined to be 160 mg/kg/day, based on reduced fetal weights among the high-dose group animals (Hoberman, 1989).

Another OECD 414 GLP gavage prenatal developmental toxicity study was conducted on groups of 25 pregnant female New Zealand White rabbits/group. The animals were administered citral extra via gavage at dose levels of 0 (0.5% carboxymethylcellulose suspension in drinking water [with 0.5 mg Tween 80/100 mL]), 20, 60, or 200 mg/kg/day on GDs 6–28. At terminal sacrifice on GD 29, 17–24 females per group had implantation sites. Mortality was reported among the high-dose group does, and gross pathological examination revealed reddening of the stomach mucosa and multiple ulcerations. Clinical observations in the high-dose group animals included reduced average food consumption and net bodyweight loss. One high-dose female had 4 dead fetuses at termination, which was considered an expression of maternal toxicity in rabbits. This was related to the local irritating potential of the test material on the gastrointestinal tract. One high-dose group doe was reported to have litters with malrotated limbs; however, this was considered to be secondary to maternal toxicity, since the doe was reported to have a significant bodyweight loss (766.5 g; 192.9 g average [net] weight loss in the high-dose group) and reduced food consumption. There were no other reported effects of treatment on the developing fetus. Considering this, there was sufficient evidence that these fetal findings were a direct consequence of severe maternal toxicity. Therefore, the NOAEL for maternal toxicity was determined to be 60 mg/kg/day based on reduced food consumption, distinct bodyweight loss, mortality, and abortion in the most sensitive individuals in the 200 mg/kg/day group. The NOAEL for prenatal developmental toxicity was determined to be 60 mg/kg/day, based on fetal mortality and limb malrotations in the 200 mg/kg/day group (RIFM, 2016a).

The developmental toxicity study on rats (Nogueira, 1995) was not considered towards determining the NOAEL since the incidences of resorptions without any visceral alterations in fetuses were reported in the presence of maternal toxicity. Similar effects on the developing fetuses were not reported among rabbits treated at comparable doses during the OECD 414 study (RIFM, 2016a) or rats during the OECD 421 study (MHW, 1996). The NOAEL for the developmental toxicity endpoint was considered to be 60 mg/kg/day as determined from the most recent and well-conducted OECD/GLP 414 developmental toxicity study on rabbits (RIFM, 2016a; ECHA, 2011).

Therefore, the farnesal MOE for the developmental toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to citral, 60/0.00010 or 600000.

The OECD 421 (MHW, 1996) and the reproductive toxicity screening study (Hoberman, 1989) conducted on citral did not show any adverse effects towards the male or the female reproductive study. The NOAEL for reproductive toxicity was determined to be 1000 mg/kg/day.

Therefore, the farnesal MOE for the reproductive toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to farnesal, 1000/0.00010 or 10000000.

In addition, the total systemic exposure to citral (0.10 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: Jackson (1987); Dieter (1993); Hagan (1967); Bar (1967); Abramovici (1983); Sandbank (1988); Abramovici (1985); RIFM, 1958; Leach (1956); Shillinger (1950); Abramovici (1980); Toaff (1979); Howes (2002); Geldof (1992); Servadio (1986a); Servadio (1986b); Servadio (1987); Abramovici (1987); Scolnik (1994a); Scolnik (1994b); Engelstein (1996); Kessler (1998); Golomb (2001); Diliberto (1988a); Diliberto (1990); Diliberto (1989); Diliberto (1988b); Ishida (1989); Boyer (1990); Phillips (1976); Barbier (1983).

Literature Search and Risk Assessment Completed On: 10/05/20.

11.1.4. Skin sensitization

Based on the material-specific data and read-across to citral (CAS # 5392-40-5), farnesal is considered to be a weak skin sensitizer with a defined NESIL of 1400 μg/cm^2.

11.1.4.1. Risk assessment. Based on the target data and read-across analog citral (CAS # 5392-40-5; see Section VI), farnesal is considered to be a weak skin sensitizer with a defined NESIL of 1400 μg/cm^2 (see Table 1). 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

Table 1
Data Summary for citral as read-across for farnesal.

LLNA weighted mean EC3 value [No. Studies] μg/cm^2	Potency Classification Based on Animal Data[b]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[c] (induction)< μg/cm^2	WoE NESIL[d] μg/cm^2
1414 [11] 2925 [1][a]	Weak	1400	NA	3876	1400

LLNA = Local lymph node assay; NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[a] Indicates EC3 value for farnesal.
[b] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[c] Data derived from HRIPT or HMT.
[d] WoE NESIL limited to 2 significant figures.

Api et al. (RIFM, 2008a; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 0.6 mg/kg/day.

Additional References: Brulos (1977); Sharp (1978); Maisey (1986); RIFM, 1982a; RIFM, 1974a; RIFM, 1974b; RIFM, 1972a; RIFM, 1971a; RIFM, 1971b; Klecak (1977); Steltenkamp (1980); Ishihara (1986); RIFM, 1974c; RIFM, 1971c; Johnson (1985); Goodwin (1985); RIFM, 1973; RIFM, 1972b; RIFM, 1972c; RIFM, 1972d; RIFM, 1964a; RIFM, 1964b; RIFM, 1965; Basketter (1991a); Basketter (1991b); Basketter (1992); Hatao (1995); Coutant (1999); Watanabe (2001); Basketter (2002); RIFM, 2002; RIFM, 2003a; RIFM, 2003b; RIFM, 2003c; RIFM, 2003d; RIFM, 2003e; RIFM, 2003f; RIFM, 2003g; RIFM, 2003h; RIFM, 2003i; Basketter (2003); Klecak (1985); RIFM, 2003j; Lalko (2004a); RIFM, 2004a; RIFM, 2004b; RIFM, 1982b; Lalko (2004b); Takeyoshi (2005); Lalko (2006); RIFM, 2005a; RIFM, 2005b; Patlewicz (2003); Piccotti (2007); Azam (2005); EPA, 1972; RIFM, 1984; RIFM, 1977; RIFM, 1981a; RIFM, 1981b.

Literature Search and Risk Assessment Completed On: 10/12/20.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/VIS absorption spectra and existing data, farnesal would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Phototoxicity of topically-applied 5% farnesal in ethanol was evaluated in Dunkin Hartley guinea pigs, and there were no observed effects (RIFM, 1985). In a separate study, photoallergy was evaluated in guinea pigs that were topically induced with undiluted farnesal and topically challenged with 5% farnesal. There were no photoallergic reactions (RIFM, 1985). Based on the *in vivo* phototoxicity and photoallergenicity studies and the lack of absorbance, farnesal would not be expected to present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/05/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for farnesal 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 farnesal. Based on the Creme RIFM Model, the inhalation exposure is 0.0030 mg/day. This exposure is 467 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/20/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

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

11.2.2. Risk assessment

Based on current VoU (2015), farnesal does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Farnesal has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

The RIFM PNEC is 0.000166 μg/L. The revised PEC/PNECs for EU and NA (use not reported) 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: 03/31/20.

12. Literature Search*

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

Search keywords: CAS number and/or material names.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.166			1000000	0.000166	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.74	5.74
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	Not Reported
Risk Characterization: PEC/PNEC	**<1**	**NA**

*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 03/31/20.

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.

Appendix A. Supplementary data

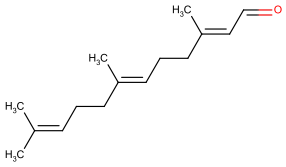
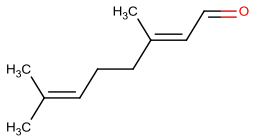
Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.111996.

Appendix

Read-across Justification

Methods

- The identified read-across analog was confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and read-across analog were calculated using EPI Suite v4.11 (US EPA, 2012a).
- The J_{max} values were calculated using the RIFM skin absorption model (SAM), and the parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification were estimated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.6 (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	3,7,11-trimethyl-2,6,10-Dodecatrienal	Citral (3,7-dimethyl-2,6-Octadienal)
CAS No.	19317-11-4	5392-40-5
Structure		
Similarity (Tanimoto score)		0.8353
Read-across Endpoint		• Genotoxicity • Repeated dose Toxicity • Developmental and Reproductive Toxicity • Skin Sensitization
Molecular Formula	$C_{15}H_{24}O$	$C_{10}H_{16}O$
Molecular Weight	220.36	152.24
Melting Point (°C, EPI Suite)	16.65	−26.74
Boiling Point (°C, EPI Suite)	302.17	217.44
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.232	12.2
Log $_{Kow}$ (KOWWIN v1.68 in EPI Suite)	5.74	3.00[1]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.4278	1340
J_{max} (μg/cm^2/h, SAM)	3.034	119.841
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.63E+002	3.81E+001
Genotoxicity		
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• Nucleophilic addition to carbonyl compounds • Schiff base formation	• Nucleophilic addition to carbonyl compounds • Schiff base formation
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Carcinogen (low reliability)	• Carcinogen (low reliability)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
***In vitro* Mutagenicity (Ames test) alerts by ISS**	• α,β-unsaturated carbonyls	• α,β-unsaturated carbonyls
***In vivo* mutagenicity (Micronucleus) alerts by ISS**	• α,β-unsaturated carbonyls	• α,β-unsaturated carbonyls
Oncologic Classification	• Aldehyde type compounds	• Aldehyde type compounds
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
Skin Sensitization		
Protein binding by OASIS v1.1	• Michael addition • Schiff base formation	• Michael addition • Schiff base formation
Protein binding by OECD	• Schiff base formers	• Schiff base formers
Protein binding potency	• Moderately reactive (GSH)	• Moderately reactive (GSH)
Protein binding alerts for skin sensitization by OASIS v1.1	• Schiff base formation	• Schiff base formation
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (Experimental value)	• Sensitizer (Experimental value)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	• See Supplemental Data 1	• See Supplemental Data 2

1 (RIFM, 2006).

Summary

There is insufficient toxicity data on farnesal (3,7,11-trimethy-2,6,10-dodecatrienal) (CAS # 19317-11-4). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, citral (3,7-dimethyl2,6-octadienal) (CAS # 5392-40-5) was identified as a read-across material with sufficient toxicological data.

Conclusions

- Citral (3,7-dimethyl-2,6-octadienal) (CAS # 5392-40-5) was used as a structurally similar read-across analog for the target material farnesal (3,7,11-trimethy-2,6,10-dodecatrienal; CAS # 19317-11-4) for the skin sensitization, genotoxicity, developmental and reproductive toxicity, and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of ketones.
  - o The target material and the read-across analog have the 3,7-dimethyl-2,6-octadienal sub-structure common among them. Both the target material and the read-across analog are α,β-unsaturated aldehydes with a β-methyl substitution, so the reactivity of the α,β-unsaturated aldehyde group and Schiff base formation for both the target material as well as the read-across analog will be the same.
  - o The key difference between the target material and the read-across analog is between the extended fragments attached to the ketone. The target material has 3,7-dimethyl-2,6-octadiene while the read-across analog has 3,7,11-trimethyl-2,6,10-dodecane as the extended aliphatic fragments. This structural difference between the target material and the read-across analog does not raise additional structural alerts, so the structural differences are not relevant from skin sensitization, genotoxicity, developmental and reproductive toxicity, and repeated dose toxicity endpoint perspectives.
  - o The read-across analog has a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the common extended fragment and ketone group. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicological endpoint perspective.
  - 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. The J_{max} value of the target material and the read-across analog appear to be different; however, with the calculated J_{max}, the read-across analog and the target material are predicted to have skin absorption either up to 80% and 40%, respectively. Other differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant for the respective toxicological endpoints.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for skin sensitization, genotoxicity, developmental and reproductive toxicity, and repeated dose toxicity are consistent between the target material and the read-across analog.
  - o According to the ISS model for carcinogenicity, the target material and read-across analog are predicted to be carcinogens with low reliability. In addition, the target material and read-across analog are predicted to be α,β-unsaturated carbonyls and can cause Schiff base formation. The data described in the genotoxicity section above describes how the read-across substance poses no concern for genetic toxicity. Therefore, the alert will be superseded by the availability of data.
  - o According to the CAESAR model, both the read-across analog and the target material are predicted to be sensitizers. In addition, the target material and read-across analog show alerts for Schiff base formation, Michael additions, and being moderately reactive. Data described above in the skin sensitization section show that the read-across material does not present a concern for skin sensitization. Therefore, the prediction will be superseded by the data.
  - 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 skin sensitization, genotoxicity, developmental and reproductive toxicity, and repeated dose toxicity are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant.

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