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RIFM fragrance ingredient safety assessment, 4,8-dimethyl-4,9-decadienal, CAS Registry Number 71077-31-1

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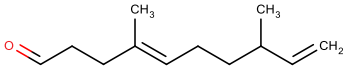

Abbreviation/Definition List:

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., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

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LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

4,8-Dimethyl-4,9-decadienal 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 citronellal (CAS # 106-23-0) show that 4,8-dimethyl-4,9-decadienal is not expected to be genotoxic. Data on 4,8-dimethyl-4,9-decadienal provided a NESIL of 550 μg/cm^2 for the skin sensitization endpoint. Data on read-across analog citral (CAS # 5392-40-5) provided a calculate MOE > 100 for the repeated dose toxicity and the developmental and reproductive toxicity endpoints. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 4,8-dimethyl-4,9-decadienal is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material and the exposure to 4,8-dimethyl-4,9-decadienal is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 4,8-dimethyl-4,9-decadienal was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(Gomes-Carneiro et al., 1998; RIFM, 2008b; RIFM, 2016a)
Repeated Dose Toxicity: NOAEL = 20 mg/kg/day.	(Ress et al., 2003)
Developmental and Reproductive Toxicity: NOAEL = 60 mg/kg/day and 1000 mg/kg/day, respectively.	(RIFM, 2016b; Ministry of Health and Welfare, 1996)
Skin Sensitization: NESIL = 550 μg/cm^2.	RIFM, (2007)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 2.82 (BIOWIN 3)	(EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 358 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 48 h *Daphnia magna* LC50: 0.29 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.29 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.029 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1	

1. Identification

1. **Chemical Name:** 4,8-Dimethyl-4,9-decadienal
2. **CAS Registry Number:** 71077-31-1
3. **Synonyms:** 4,9-Decadienal, 4,8-dimethyl-; Floral Super; Aldehyde DMD; 4,8-Dimethyl-4,9-decadienal
4. **Molecular Formula:** $C_{12}H_{20}O$
5. **Molecular Weight:** 180.29
6. **RIFM Number:** 5961

2. Physical data

1. **Boiling Point:** 241.28 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS)
3. **Log K_{OW}:** 4.38 (EPI Suite)
4. **Melting Point:** −7.37 °C (EPI Suite)
5. **Water Solubility:** 10.05 mg/L (EPI Suite)
6. **Specific Gravity:** Not available
7. **Vapor Pressure:** 0.0433 mm Hg @ 25 °C (EPI Suite), 0.0277 mm Hg @ 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless to pale yellow, clear, liquid with a medium floral, aldehydic, magnolia, lily odor

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics*:** 0.0029% (RIFM, 2014a)
3. **Inhalation Exposure**:** 0.000071 mg/kg/day or 0.0054 mg/day (RIFM, 2014a)
4. **Total Systemic Exposure***:** 0.00067 mg/kg/day (RIFM, 2014a)

*See IFRA Category 4 in Section 9 for maximum acceptable concentrations in finished products.

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

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. **Analogs Selected:**
   a. **Genotoxicity:** Citronellal (CAS # 106-23-0)
   b. **Repeated Dose Toxicity:** Citral (CAS # 5392-40-5)
   c. **Developmental and Reproductive Toxicity:** Citral (CAS # 5392-40-5)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

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

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

4,8-Dimethyl-4,9-decadienal is not reported to occur in food by the VCF*.

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

8. REACH dossier

Available; accessed 04/22/19 (ECHA, 2016a).

9. Conclusion

The maximum acceptable concentrations[a] in finished products for 4,8-dimethyl-4,9-decadienal are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.000060
2	Products applied to the axillae	0.013
3	Products applied to the face/body using fingertips	0.042
4	Products related to fine fragrances	0.24
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.060
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.060
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.060
5D	Baby cream, oil, talc	0.020
6	Products with oral and lip exposure	0.000060
7	Products applied to the hair with some hand contact	0.38
8	Products with significant ano-genital exposure (tampon)	0.020
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.46
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.46
10B	Aerosol air freshener	1.7
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.020
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	100

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 4,8-dimethyl-4,9-decadienal, 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 550 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and usage levels, 4,8-dimethyl-4,9-decadienal does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 4,8-Dimethyl-4,9-decadienal was tested using the BlueScreen assay and found not to be genotoxic with or without S9 metabolic activation, indicating a lack of concern regarding genotoxicity RIFM, 2013). There are no studies assessing the mutagenic activity of 4,8-dimethyl-4,9-decadienal. The mutagenic potential of read-across material citronellal (CAS # 106-23-0; see Section 5) was assessed in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the revised plate incorporation method of Maron and Ames (Maron et al., 1981). *Salmonella typhimurium* strains TA97a, TA98, TA100, and TA102 were treated with citronellal in ethanol at concentrations up to 300 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (Gomes-Carneiro et al., 1998). Under the conditions of the study, citronellal was not mutagenic in the Ames test. A mammalian cell gene mutation assay (HPRT) was also conducted according to OECD TG 476 and GLP guidelines. Chinese hamster lung cells (V79) were treated with citronellal in dimethyl sulfoxide (DMSO) at concentrations up to 128 μg/mL for 4 h. Effects were evaluated both with and without metabolic activation. No significant increases in the frequency of mutant colonies were observed with any dose of the test material, either with or without metabolic activation (RIFM, 2008b).

There are no studies assessing the clastogenicity of 4,8-dimethyl-4,9-decadienal. Read-across material citronellal was assessed for clastogenic activity in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with citronellal in DMSO at concentrations up to 1540 μg/mL in the presence and absence of metabolic activation (S9) at the 4-h and 24-h time points. Citronellal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems at the 4-h time point. A statistically significant increase (Fisher's exact test) in binucleated cells with micronuclei was observed at the 24-h time point without S9-activation but these increases were not dose-dependent. In order to confirm the effects observed at the 24-h time point and also to comply with new OECD 487 guidelines adopted on September 26, 2014, the assay was repeated for a 24-h non-activated treatment condition. Citronellal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in the non-activated test system at the 24-h time point (RIFM, 2016a). Under the conditions of the study, citronellal was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, citronellal does not present a concern for genotoxic potential and this can be extended to 4, 8-dimethyl-4,9-decadienal.

Additional References: Kasamaki et al., 1982; Sasaki et al., 1989; Carneiro et al., 1997; Oda et al., 1978; RIFM, 2014b.

Literature Search and Risk Assessment Completed On: 09/08/16.

10.1.2. Repeated dose toxicity

The MOE for 4,8-dimethyl-4,9-decadienal is adequate for repeated dose toxicity at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4,8-dimethyl-4,9-decadienal. The read-across analog citral (CAS # 5392-40-5; see Section 5) has sufficient repeated dose toxicity data. A National Toxicology Program (NTP)-sponsored chronic dietary study was conducted in compliance with GLP on groups of 50 F344/N rats/sex/group. The animals were administered the test material 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 et al., 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 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 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 (Ress et al., 2003; [data also available in National Toxicology Program, 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 4,8-dimethyl-4,9-decadienal 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 4,8-dimethyl-4,9-decadienal, 20/0.00067 or 29851.**

In addition, the total systemic exposure to 4,8-dimethyl-4,9-decadienal (0.67 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1.1. Derivation of reference dose (RfD). Section 9 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, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.6 mg/kg/day.

The RfD for 4,8-dimethyl-4,9-decadienal was calculated by dividing

the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive 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 Derived No Effect Level for citral for General Population - Hazard via oral route (ECHA, 2011; accessed 08/01/17).

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

Literature Search and Risk Assessment Completed On: 12/23/16.

10.1.3. Developmental and reproductive toxicity

The MOE for 4,8-dimethyl-4,9-decadienal is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data 4,8-dimethyl-4,9-decadienal. The read-across analog citral (CAS # 5392-40-5; see Section 5) 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 et al., 1995).

An OECD 421 gavage reproductive 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 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 (Ministry of Health and Welfare, 1996).

A reproductive toxicity screening study conducted on 30 female Sprague Dawley rats/group 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 the control. Thus, the NOAEL the developmental toxicity was determined to be 160 mg/kg/day, based on reduced fetal weights among the high-dose group animals (Hoberman et al., 1989).

Another OECD/GLP 414 GLP gavage prenatal developmental toxicity study was conducted on groups of 25 pregnant female New Zealand white rabbits/group. The animals were administered the test material 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 having malrotated limbs; however, this was considered to be secondary to maternal toxicity, since the doe was reported to have significant bodyweight loss 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, 2016b).

The developmental toxicity study on rats (Nogueira et al., 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, 2016b) or among rats during the OECD 421 study (Ministry of Health and Welfare, 1996). Thus, 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, 2016b; ECHA, 2011).

Therefore, the 4,8-dimethyl-4,9-decadienal MOE for the developmental toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to 4,8-dimethyl-4,9-decadienal, 60/0.00067 or 89552.

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

Therefore, the 4,8-dimethyl-4,9-decadienal MOE for the reproductive toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to 4,8-dimethyl-4,9-decadienal, 1000/0.00067 or 1492537.

In addition, the total systemic exposure to 4,8-dimethyl-4,9-decadienal (0.67 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

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

Literature Search and Risk Assessment Completed On: 12/23/16.

Table 1
Data summary for 4,8-dimethyl-4,9-decadienal.

Local Lymph Node Assay Weighted Mean EC3 Value μg/cm[b] (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (Induction) μg/cm[b]	NOEL-HMT (Induction) μg/cm[b]	LOEL[b] (Induction) μg/cm[b]	WoE NESIL[c] μg/cm[b]
NA	Weak	551	NA	NA	550

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.

[c] WoE NESIL limited to 3 significant figures.

10.1.4. Skin sensitization

Based on the existing data, 4,8-dimethyl-4,9-decadienal is considered a weak sensitizer with a defined NESIL of 550 μg/cm^2.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to significantly react with skin proteins (Toxtree 2.6.6; OECD toolbox v3.3). In a guinea pig sensitization study, 5% induction with 4,8-dimethyl-4,9-decadienal produced sensitization reactions upon challenge with 5%, 10%, and 20% of the material in liquid paraffin (RIFM, 1982). In a confirmatory human repeat insult patch test (HRIPT), 4,8-dimethyl-4,9-decadienal did not induce sensitization reactions at 1% or 551 μg/cm^2 in 113 subjects (RIFM, 2007).

Based on the WoE from structural analysis and animal and human studies, 4,8-dimethyl-4,9-decadienal is a sensitizer with a WoE NESIL of 550 μg/cm^2 (Table 1). Section 9 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, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.6 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/09/16.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 4,8-dimethyl-4,9-decadienal would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 4,8-dimethyl-4,9-decadienal in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 4,8-dimethyl-4,9-decadienal does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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, 1000 L mol^{-1} · cm^{-1}, of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/12/16.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to lack of appropriate data. The exposure level for 4,8-dimethyl-4,9-decadienal is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 4,8-dimethyl-4,9-decadienal. Based on the Creme RIFM Model, the inhalation exposure is 0.0054 mg/day. This exposure is 259.3 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: 03/20/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 4,8-dimethyl-4,9-decadienal was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 4,8-dimethyl-4,9-decadienal was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 4,8-dimethyl-4,9-decadienal as possibly being persistent or bioaccumulative based on its structure and physical–-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is

determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current VoU (2015), 4,8-dimethyl-4,9-decadienal presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.3.1.1. Biodegradation. No data available.

10.2.3.1.2. Ecotoxicity. No data available.

10.2.3.1.3. Other available data. 4,8-Dimethyl-4,9-decadienal has been registered under REACH and additional data is available.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.074			1000000	0.002074	
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	0.587	0.290	0.757	10000	0.029	Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	1.087	0.769	1.419			Neutral Organic SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.38	4.38
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.029 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 03/14/19.

11. 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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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.

*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 04/22/19.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

☒ 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.2019.110648.

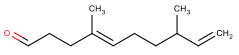
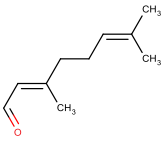
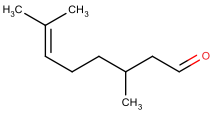
Appendix

Read-across Justification

Methods

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

- 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 and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	4,8-Dimethyl-4,9-decadienal	2,6-Octadienal, 3,7-dimethyl	Citronellal
CAS No.	71077-31-1	5392-40-5	106-23-0
Structure			
Similarity (Tanimoto Score)		0.821	0.617
Read-across Endpoint		• Repeated dose • Developmental and Reproductive	• Genotoxicity
Molecular Formula	$C_{12}H_{20}O$	$C_{10}H_{16}O$	$C_{10}H_{18}O$
Molecular Weight	180.91	152.24	154.25
Melting Point (°C, EPI Suite)	−7.37	−26.74	−28.33
Boiling Point (°C, EPI Suite)	241.28	217.44	207
Vapor Pressure (Pa @ 25 °C, EPI Suite)	5.77	12.2	33.9
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	4.38	3.00[1]	3.83
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	10.05	1340	38.94
J_{max} (μg/cm^2/h, SAM)	7.448	109.370	52.350
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.04E+001	3.81E+001	6.88E+001
Genotoxicity			
DNA Binding (OASIS v1.4 QSAR Toolbox v3.4)	• No alert found		• No alert found
DNA Binding by OECD QSAR Toolbox (v3.4)	• Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes		• Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Carcinogen (low reliability)		• Carcinogen (moderate reliability)
DNA Alerts for Ames, MN, CA by OASIS v1.1	• No alert found		• No alert found
In vitro Mutagenicity (Ames test) alerts by ISS	• Simple aldehyde		• Simple aldehyde

In vivo mutagenicity (Micronucleus) alerts by ISS	• Simple aldehyde		• Simple aldehyde
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)	
Metabolism			
OECD QSAR Toolbox (3.4) Rat Liver S9 Metabolism Simulator	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 4,8-dimethyl-4,9-decadienal (CAS # 71077-31-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analogs citral (2,6-octadienal, 3,7-dimethyl) (CAS # 5392-40-5) and citronellal (CAS # 106-23-0) were identified as read-across materials with sufficient toxicological data.

Conclusions

- Citral (2,6-octadienal, 3,7-dimethyl) (CAS # 5392-40-5) can be used as a structurally similar read-across analog for the target material 4,8-dimethyl-4,9-decadienal (CAS # 71077-31-1) for the 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 aldehydes.
  - o The target material and the read-across analog have the 1-methyl-hept-1-ene fragment common among them.
  - o The key difference between the target material and the read-across analog is that the read-across an α,β-unsaturated aldehyde, while the target material does not have α-β unsaturation to the aldehyde group. Because the read-across analog has an activated aldehyde group, it will form a direct-acting Schiff base and be a Michael acceptor, therefore raising toxicity compared to the target material for systemic toxicity endpoints and will be more reactive for the developmental and reproductive toxicity and repeated dose toxicity endpoint perspective.
  - o The target material and the read-across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the 1-methyl hex-1-ene fragment. The differences in the structure which are responsible for a Tanimoto score < 1 are not relevant from a toxicity endpoint perspective.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. The J_{max} value of the target and the read-across analog appear to be different; 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 Any 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 respiratory toxicity, developmental and reproductive toxicity, and repeated dose toxicity endpoints.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the respiratory toxicity, developmental and reproductive toxicity, and repeated dose toxicity endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for the respiratory toxicity, developmental and reproductive toxicity, and repeated dose toxicity endpoints 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.
- Citronellal (CAS # 106-23-0) can be used as a structurally similar read-across analog for the target material 4,8-dimethyl-4,9-decadienal (CAS # 71077-31-1) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The target material and the read-across analog have the α-substituted aldehyde and unsaturated branched hydrocarbon chain.
  - o The key difference between the target material and the read-across analog is that the target material has a higher degree of unsaturation and a longer aliphatic chain compared to the read-across analog, as well as a terminal vinyl group. This structural difference between the target material and the read-across analog do not raise additional structural alerts, so the structural differences are not relevant from a toxicity endpoint perspective.
  - o The target material and the read-across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the α-substituted aldehyde and unsaturated isopropyl group. The differences in the structure which are responsible for a Tanimoto score < 1 are not relevant from a toxicity endpoint perspective.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. The J_{max} value of the target material and the read-across analog appear to be different; with the calculated J_{max}, the read-across analog substance and the target 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 the genotoxicity endpoint are consistent between the target material and the read-across analog.
  - o According to the ISS model for carcinogenicity, the target material and the read-across analog are predicted to be carcinogens with low reliability and moderate reliability, respectively. In addition, the target material and the read-across analog are predicted to be simple aldehyde and Schiff base formers. The data described in the genotoxicity section above show that the read-across analog poses no concern for

genotoxicity. Therefore, the alert will be superseded by the availability of 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 the genotoxicity endpoint 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.

Explanation of Cramer Classification

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q16. Common terpene? No.
Q17. Readily hydrolyzed to a common terpene? No.
Q20. Aliphatic with some functional groups (see explanation)? Yes.
Q 21. Three or more different functional groups? No.
Q1 8. One of the list (see explanation) No. Class Low (Class I).

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