Food and Chemical Toxicology 141 (2020) 111384

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

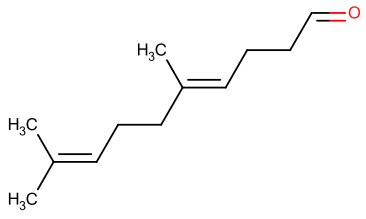
RIFM fragrance ingredient safety assessment, 5,9-dimethyl-4,8-decadienal, CAS Registry Number 762-26-5

A.M. Api[a], D. Belsito[b], S. Biserta[a], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.A. Cancellieri[a], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], A.D. Fryer[h], S. Gadhia[a], L. Jones[a], K. Joshi[a], A. Lapczynski[a], M. Lavelle[a], D.C. Liebler[i], M. Na[a], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], F. Rodriguez-Ropero[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], F. Siddiqi[a], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

Version: 060619. This version replaces any previous versions.

Name: 5,9-Dimethyl-4,8-decadienal
CAS Registry Number: 762-26-5



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

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2020.111384
Received 9 July 2019; Received in revised form 16 March 2020; Accepted 19 April 2020
Available online 28 April 2020
0278-6915/

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
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.

5,9-Dimethyl-4,8-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 citral (CAS # 5392-40-5) show that this material is not expected to be genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and the developmental and reproductive toxicity endpoints. Data on read-across analog citronellal (CAS # 106-23-0) provided 5,9-dimethyl-4,8-decadienal a No Expected Sensitization Induction Level (NESIL) of 7000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 5,9-dimethyl-4,8-decadienal is not expected to be 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 5,9-dimethyl-4,8-decadienal is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 5,9-dimethyl-4,8-decadienal 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 et al., 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 = 7000 μg/cm^2 — (RIFM, 1977; Robinson et al., 1990; Basketter and Gerberick, 1996; Marzulli and Maibach, 1980)
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 v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 387.5 L/kg — (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia Magna* LC50: 0.266 mg/L — (ECOSAR, v1.11; 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: 0.266 mg/L — (ECOSAR, v1.11; US EPA, 2012b)
RIFM PNEC is: 0.0266 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1

1. Identification

1. **Chemical Name:** 5,9-Dimethyl-4,8-decadienal
2. **CAS Registry Number:** 762-26-5
3. **Synonyms:** 4,8-Decadienal, 5,9-dimethyl-; Geraldehyde; 5,9-Dimethyldeca-4,8-dienal; Geranyl Acetaldehyde; 5,9-Dimethyl-4,8-decadienal
4. **Molecular Formula:** $C_{12}H_{20}O$
5. **Molecular Weight:** 180.91
6. **RIFM Number:** 5214

2. Physical data

1. **Boiling Point:** 253.84 °C (EPI Suite)
2. **Flash Point:** > 212.00 °F; TCC (> 100.00 °C)*
3. **Log K_{OW}:** 4.43 (EPI Suite)
4. **Melting Point**: 4.84 °C (EPI Suite)
5. **Water Solubility:** 9.086 mg/L (EPI Suite)
6. **Specific Gravity:** 0.86900 to 8.73000 @ 25.00 °C*
7. **Vapor Pressure:** 0.0139 mm Hg @ 20 °C (EPI Suite v4.0), 0.0222 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$).
9. **Appearance/Organoleptic:** Colorless to pale yellow clear liquid with a medium citrus, aldehydic, marine, floral, and ozone like odor if smelled in a 10.00% solution or less*

*http://www.thegoodscentscompany.com/data/rw1020071.html, retrieved 02/03/14.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.15% (RIFM, 2016b)
3. **Inhalation Exposure*:** 0.000068 mg/kg/day or 0.0049 mg/day (RIFM, 2016b)
4. **Total Systemic Exposure**:** 0.00058 mg/kg/day (RIFM, 2016b)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** Citral (mixture of *cis*- and *trans*-isomers; 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:** Citronellal (mixture of *cis*- and *trans*-isomers; CAS # 106-23-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justifications: 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)

5,9-Dimethyl-4,8-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 06/06/19.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for 5,9-dimethyl-4,8-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)	0.074
2	Products applied to the axillae	0.16
3	Products applied to the face/body using fingertips	0.074
4	Products related to fine fragrances	3.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.76

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	0.074
5D	Baby cream, oil, talc	0.025
6	Products with oral and lip exposure	0.074
7	Products applied to the hair with some hand contact	1.1
8	Products with significant ano-genital exposure (tampon)	0.025
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.5
10A	Household care products with mostly hand contact (hand dishwashing detergent)	2.5
10B	Aerosol air freshener	4.6
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.025
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 5,9-dimethyl-4,8-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 7000 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 use levels, 5,9-dimethyl-4,8-decadienal does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 5,9-Dimethyl-4,8-decadienal was assessed for genotoxic potential in the BlueScreen assay and was found negative for genotoxicity, demonstrating a lack for genotoxic potential (RIFM, 2013). There are no data assessing the mutagenic potential of 5,9-dimethyl-4,8-decadienal. The read-across material, citral (CAS # 5392-40-5; see Section V), was assessed in an Ames assay conducted according to OECD 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.

There are no data on the clastogenic activity for 5,9-dimethyl-4,8-decandienal. Read-across analog citral was assessed for clastogenicity by the National Toxicology Program (NTP). In an *in vitro* Sister Chromatid Exchange (SCE) assay according to OECD TG 479, citral was shown to induce SCEs in Chinese hamster ovary cells (CHO) with and without S9 mix at doses > 7.5 mg/mL in the presence of S9 and at all doses tested in absence of S9. A subsequent *in vitro* chromosome aberration study according to 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 citral/kg body weight in corn oil. Animals were euthanized 24 h after the third injection, and 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, and this can be extended to the target material, 5,9-dimethyl-4,8-decadienal.

Taken together, the read-across material citral does not present a concern for genotoxic potential, and this can be extended to the target material, 5,9-dimethyl-4,8-decadienal.

Additional References: ECHA, 2011; Eder et al., 1982; Ishidate et al., 1984; Lutz et al., 1982; Carneiro et al., 1997; Gomes-Carneiro et al., 1998; Zeiger et al., 1987; Kuroda et al., 1984; Yoo (1986); Duerksen-Hughes et al., 1999; Oda et al., 1978; Ishidate et al., 1984.

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

10.1.2. Repeated dose toxicity

The MOE for 5,9-dimethyl-4,8-decadienal is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 5,9-dimethyl-4,8-decadienal. Read-across material citral (CAS # 5392-40-5; see Section V) 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 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 that were 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 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. The derived NOAEL was determined to be 20 mg/kg/day (Ress et al., 2003; data also available in NTP, 2003). The most conservative NOAEL for repeated dose toxicity was determined from a dietary 104–105 week

carcinogenicity study in mice to be 20 mg/kg/day, based on reduced body weights.

Therefore, the 5,9-dimethyl-4,8-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 5,9-dimethyl-4,8-decadienal, 20/0.00058 or 34483.

In addition, the total systemic exposure to 5,9-dimethyl-4,8-decadienal (0.58 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section IX 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, 2008; 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.

10.1.2.1.1. Derivation of reference dose (RfD). The reference dose for 5,9-dimethyl-4,8-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.

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 5,9-dimethyl-4,8-decadienal is adequate for the developmental and reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on 5,9-dimethyl-4,8-decadienal. Read-across material citral (CAS # 5392-40-5; see Section V) 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 the test material, citral, at dose levels of 0 (corn oil), 60, 125, 250, 500, or 1000 mg/kg/day on gestation days 6–15. The study was terminated on gestation day 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 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 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 that 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 gestation day 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. There was, however, a significant decrease in the average pup body weight at birth among the high-dose group animals as compared to control. 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 et al., 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 gestation days (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 a 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 the 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 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, 2016a) or rats during the OECD 421 study (MHW, 1996). Therefore, 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 414/GLP developmental toxicity study on rabbits (RIFM, 2016a; ECHA, 2011).

Therefore, the 5,9-dimethyl-4,8-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 5,9-dimethyl-4,8-decadienal, 60/0.00058 or 103448.

The OECD 421 (MHW, 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 study. The NOAEL for reproductive toxicity was determined to be 1000 mg/kg/day.

Therefore, the 5,9-dimethyl-4,8-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 5,9-dimethyl-4,8-decadienal, 1000/0.00058 or 1724138.

In addition, the total systemic exposure to 5,9-dimethyl-4,8-decadienal (0.58 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and

Table 1
Data summary for citronellal.

LLNA weighted mean EC3 value [No. Studies] μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/c^2	WoE NESIL[c] μg/cm^2
> 7500 [1]	weak	7086[d]	2760[d]	NA	7000

NOEL = No observed effect level; HRIP = Human Repeat Insult Patch Tes; HMT = Human Maximization Test; LOEL = lowet 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 2 significant figures.

[d] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in HRIPT or HMT studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL.

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.

10.1.4. Skin sensitization

Based on the existing data and read-across citronellal (CAS # 106-23-0), 5,9-dimethyl-4,8-decadienal is considered to be a weak sensitizer.

10.1.4.1. Risk assessment. Based on existing data and read-across to citronellal (CAS # 106-23-0; see Section V), 5,9-dimethyl-4,8-decadienal is considered a weak skin sensitizer. The chemical structures of 5,9-dimethyl-4,8-decadienal and citronellal indicate that the materials have the potential to react with skin proteins via a Schiff base mechanism (Toxtree 2.5.0; OECD Toolbox v3.1). In a Buehler guinea pig sensitization study, no reactions indicative of sensitization were observed with 5,9-dimethyl-4,8-decadienal at 1% in alcohol SDA 39C (RIFM, 1980). However, in a guinea pig maximization test, 4 of the 8 guinea pigs exhibited reactions indicative of sensitization with 3% citronellal (RIFM, 1977). In a small subject base human confirmatory study, no sensitization reactions were observed to 5,9-dimethyl-4,8-decadienal at 1% or 500 μg/cm^2 (RIFM, 1980). Similarly, in a human repeat insult patch test (HRIPT), read-across analog citronellal did not induce sensitization reactions at 6% or 7086 μg/cm^2 (RIFM, 2014). Based on the material specific data and read-across 5,9-dimethyl-4,8-decadienal is considered to be a weak skin sensitizer with a defined NESIL of 7000 μg/cm^2 (Table 1). Section IX 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, 2008; 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: RIFM, 1981.

Literature Search and Risk Assessment Completed On: 09/21/16.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, 5,9-dimethyl-4,8-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 5,9-dimethyl-4,8-decadienal in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern, 1000 L mol^{-1} · cm^{-1}, for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 5,9-dimethyl-4,8-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 minor 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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/07/16.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 5,9-dimethyl-4,8-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 5,9-dimethyl-4,8-decadienal. Based on the Creme RIFM Model, the inhalation exposure is 0.0049 mg/day. This exposure is 286 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: 03/28/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment 5,9-dimethyl-4,8-decadienal performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity

estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 5,9-dimethyl-4,8-decadienal was identified as a fragrance material with 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 ECHA, 2012a) identified 5,9-dimethyl-4,8-decadienal as not persistent and not 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 criteria used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite models BIOWIN 2 or BIOWIN 6 < 0.5 and BIOWIN 3 < 2.2, then the material is considered as 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. Should additional assessment be required, based on these model outputs (Step 1), a weight-of-evidence based review is 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 4.11). Data on biodegradation, fate, and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on current Volume of Use (2015), 5,9-dimethyl-4,8-decadienal presents a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies. ***Biodegradation:*** No data available.

Ecotoxicity: No data available.

Other available data: 5,9-Dimethyl-4,8-decadienal has been registered under REACH and the following data is available:

A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 based on geometric mean measured concentration was 0.73 mg/L (ECHA, 2017).

An algae growth inhibition test was conducted according to the OECD 201 method. Based on geometric mean measured concentration, the 72-h EC50, EC10, and NOEC were reported to be 2.9 mg/L, 0.21 mg/L, and 0.045 mg/L, respectively (ECHA, 2017).

10.2.2. Risk assessment refinement

Since 5,9-Dimethyl-4,8-decadienal has passed the screening-level, measured data is included for completeness only and has not been used in PNEC derivation.

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)**	1.876 l			1,000,000	0.001876	
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	0.552	0.266	0.702	10,000	0.0266	Aldehydes (mono)
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	0.978	0.695	1.308			Neutral Organics SAR (baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.43	4.43
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.0266 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 volumes of use.

Literature Search and Risk Assessment Completed On: 04/03/19.

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 01/22/19.

Declaration of competing interest

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

Appendix A. Supplementary data

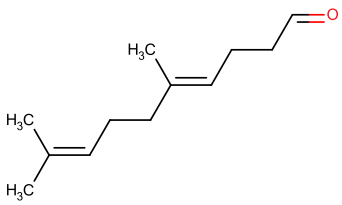
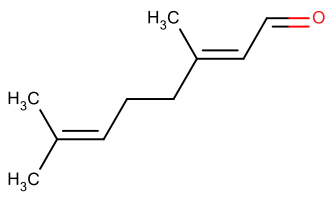
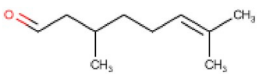
Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111384.

Appendix

Read-across Justification

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of target and analogs were calculated using EPI Suite v4.11 developed by US EPA (US ECHA, 2012).
- The J_{max} values were calculated using the RIFM skin absorption model (SAM). The parameters were calculated using 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 were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2018).

	Target material	Read-across material	Read-across material
Principal Name	5,9-Dimethyl-4,8-decadienal	Citral	Citronellal
CAS No.	762-26-5	5392-40-5	106-23-0
Structure			
Similarity (Tanimoto score)		0.887	0.856
Read-across endpoint		• Genotoxicity • Repeated dose • Developmental and Reproductive	• Skin sensitization
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)	−4.84	−26.74	−28.33
Boiling Point (°C, EPI Suite)	253.84	217.44	205.07
Vapor Pressure (Pa @ 25 °C, EPI Suite)	2.96	12.2	33.9
Log Kow (KOWWIN v1.68 in EPI Suite)	4.43	3.00[1]	3.83
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	9.086	1340	38.94
J_{max} (μg/cm^2/h, SAM)	12.008	109.370	52.35

Henry's Law ($Pa \cdot m^3/mol$, Bond Method, EPI Suite)	1.26E + 002	3.81E + 001	6.88E + 001
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• AN2, Nucleophilic addition to carbonyl compounds • Schiff base formation	
DNA binding by OECD QSAR Toolbox (3.4)	• Schiff base formers	• No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Carcinogen (low reliability)	• Carcinogen (moderate 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	• Simple aldehyde	• α,β-unsaturated carbonyls	
In vivo mutagenicity (Micronucleus) alerts by ISS	• Simple aldehyde	• 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	• Schiff base formation		• Schiff base formation
Protein binding by OECD	• Schiff base formers		• Schiff base formers
Protein binding potency	• Not possible to classify		• Not possible to classify
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 (good reliability)		• Sensitizer (good reliability)
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

1 (RIFM, 2006):

Summary

There is insufficient toxicity data on 5,9-dimethyl-4,8-decadienal (CAS # 762-26-5). 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 (CAS # 5392-40-5) and citronellal (CAS # 106-23-0) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Citral (2,6-octadienal, 3,7-dimethyl) (CAS # 5392-40-5) could be used as structurally similar read-across analog for the target material 5,9-dimethyl-4,8-decadienal (CAS # 762-26-5) for the genotoxicity, developmental and reproductive toxicity, and repeated dose toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The target substance and the read-across analog have the 1-methyl-hept-1-ene common among them.
  - o The key difference between the target substance and the read-across analog is that the read-across is an α,β-unsaturated aldehyde while the target 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, it will be more reactive compared to the target.
  - o The target substance and the read-across analog have Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the aldehyde group and the 1-methyl-hept-1-ene extended fragment at the tail end of the molecules. The differences in the structure responsible for the Tanimoto score < 1 are not relevant from a toxicity endpoint perspective.
  - o The target substance and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target substance and the read-across analog are estimated to be toxicologically insignificant.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for genotoxicity, reproductive and developmental toxicity, and repeated dose toxicity are consistent between the target substance and the read-across analog.
  - o According to ISS model for carcinogenicity, the target material and read-across analog citral are predicted to be carcinogens with low reliability. In addition, the target material is predicted to be Schiff base former and simple aldehyde, and the read-across analog is predicted to be an α,β-unsaturated carbonyl and can cause Schiff base formation. The data described in the genetic toxicity section above describes that the read-across substance poses no concern for genotoxicity. Therefore, the alert will be superseded by the availability of data.
  - o According to the metabolic simulator, the read-across analog is expected to undergo metabolism and form Schiff base at the activated aldehyde group. The target substance will not have similar metabolism as seen for the read-across analog.
  - o The structural alerts for the genotoxicity, reproductive and developmental toxicity, and repeated dose toxicity are consistent between the metabolites of the read-across analog and the target substance.
  - o The structural differences between the target substance and the read-across analog are deemed to be toxicologically insignificant.
- Citronellal (6-octenal, 3,7-dimethyl) (CAS # 106-23-0) could be used as a structurally similar read-across analog for the target material 5,9-dimethyl-4,8-decadienal (CAS # 762-26-5) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The target substance and the read-across analog have the α-substituted aldehyde and unsaturated isopropyl group at the tail end common among them.

- o The key difference between the target substance and the read-across analog is that the target substance has an additional vinyl group compared to the read-across analog. This structure difference between the target substance and the read-across analog does not raise additional structural alerts, so the structure differences are not relevant from the skin sensitization endpoint perspective.
- o The target substance 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 Tanimoto score < 1 are not relevant from a toxicity endpoint perspective.
- o The target substance and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target substance and the read-across analog are estimated to be toxicologically insignificant for the skin sensitization endpoint.
- o According to the QSAR OECD Toolbox (V3.4), structural alerts for skin sensitization endpoint are consistent between the target substance and the read-across analog.
- o According to the CAESAR model, both the read-across analog and the target substance are predicted to be sensitizers. In addition, the target material and read-across analog show alerts for Schiff base formation. Data described above in the skin sensitization section confirms, based on the existing data and read-across, that the target is considered to be a weak sensitizer. Therefore, the *in silico* alerts agree with data.
- o The target substance and the read-across analog are expected to be metabolized similarly as shown by metabolism simulator.
- o The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read-across analog and the target substance.
- o The structural differences between the target substance and the read-across analog are deemed to be toxicologically insignificant.

References

Abramovici, A., Feder, J., 1980. Embryotoxic effect of citral in chick and rat embryos as related to their detoxificative capacity. Acta Morphol. Acad. Sci. Hung. 28 (1–2), 203.

Abramovici, A., Servadio, C., Sandbank, U., 1985. Benign hyperplasia of ventral prostate in rats induced by a monoterpene (preliminary report). Prostate 7, 389–394.

Abramovici, A., Servadio, C., Shmuely, J., Sandbank, U., 1987. Experimental induction of atypical hyperplasia in rat ventral prostate. In: Prostate Cancer. Part A, Res., Endocrine Treatment & Histopathology, pp. 559–568.

Abramovici, A., Wolf, R., Sandbank, M., 1983. Sebaceous glands changes following topical application of citral. Acta Dermato-Venereologica. Stockh. 428–431.

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Bar, V.F., Griepentrog, F., 1967. Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel Fur Lebensmittel. (Where we stand concerning the evaluation of flavoring substances from the viewpoint of health). Medizin Ernahr 8, 244–251.

Barbier, P., Benezra, C., 1983. The influence of limonene on induced delayed hypersensitivity to citral in Guinea pigs. II. Label distribution in the skin of 14C-labelled citral. Acta Dermato-Venereologica. Stockh. 63, 93–96.

Basketter, D.A., Gerberick, G.F., 1996. An interlaboratory evaluation of the Buehler test for the identification and classification of skin sensitizers. Contact Dermatitis 35 (3), 146–151.

Boyer, S.C., Petersen, D.R., 1990. The metabolism of 3,7-dimethyl-2,6-octandienal (citral) in rat hepatic mitochondrial and cytosolic fractions. Drug Metabol. Dispos. 18, 81–86.

Carneiro, M.R.G., Paumgartten Jr., F., Felzenswalb, I., 1997. Evaluation of the mutagenic potential of monoterpenoid compounds. Mutat. Res. Fund Mol. Mech. Mutagen 379 (1 Suppl. 1), S110.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Dieter, M.P., Goehl, T.J., Jameson, C.W., Elwell, M.R., Hildebrandt, P.K., Yuan, J.H., 1993. Comparison of the toxicity of citral in F344 rats and B6C3F1 mice when administered by microencapsulation in feed or by corn-oil gavage. Food Chem. Toxicol. 31 (7), 463–474.

Diliberto, J.J., Srinivas, P., Burka, L.T., Birnbaum, L.S., 1989. In vivo metabolism of cis and trans 3,7-dimethyl-2,6-octadienal (citral) in rats. Toxicologist 9 (1), 87.

Diliberto, J.J., Srinivas, P., Overstreet, D., Usha, G., Burka, L.T., Birnbaum, L.S., 1990. Metabolism of citral, an alpha,beta-unsaturated aldehyde, in male F344 rats. Drug Metabol. Dispos. 18 (6), 866–875.

Diliberto, J.J., Usha, G., Birnbaum, L.S., 1988a. Dispositon of citral in male Fischer rats. Drug Metabol. Dispos. 16 (5), 721–727.

Diliberto, J.J., Usha, G., Burka, L.T., Birnbaum, L.S., 1988b. Biotransformation of citral in rats. Toxicologist 8 (1), 208.

Duerksen-Hughes, P.J., Yang, J., Ozcan, O., 1999. p53 Induction as a genotoxic test for twenty-five chemicals undergoing in vivo carcinogenicity testing. Environ. Health Perspect. 107 (10), 805–812.

ECHA, 2011. Citral registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/13515/1.

ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2017. 5,9-Dimethyl-4,8-decadienal registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/20464/1.

Eder, E., Henschler, D., Neudecker, T., 1982. Mutagenic properties of allylic and alpha, beta-unsaturated compounds: consideration of alkylating mechanisms. Xenobiotica 12 (12), 831–848.

Engelstein, D., Shmueli, J., Bruhis, S., Servadio, C., Abramovici, A., 1996. Citral and testosterone interactions in inducing benign and atypical prostatic hyperplasia in rats. Comp. Biochem. Physiol. 115 (2), 169–177.

Geldof, A.A., Engel, C., Rao, B.R., 1992. Estrogenic action of commonly used fragrant agent citral induces prostatic hyperplasia. Urol. Res. 20 (2), 139–144.

Golomb, E., Scolnik, M., Koren, R., Servadio, C., Sandbank, U., Abramovici, A., 2001. Effects of senescence and citral on neuronal vacuolar degeneration in rat pelvic ganglia. Neurotoxicology 22 (1), 73–77.

Gomes-Carneiro, M.R., Felzenszwalb, I., Paumgartten, F.J.R., 1998. Mutagenicity testing of (+/-)-camphor, 1,8-cineole, citral, citronellal, (-)-menthol and terpineol with the Salmonella/microsome assay. Mutation Research. Genet. Toxicol. Environ. Mutagen 416 (1–2), 129–136.

Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.M., Brouwer, J.B., 1967. Food flavorings and compounds of related structure. II. Subacute and chronic toxicity. Food Chem. Toxicol. 5 (2), 141–157.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

Hoberman, A.M., Christian, M.S., Bennett, M.B., Vollmuth, T.A., 1989. Oral general reproduction study of citral in female rats. Toxicologist 9 (1), 271.

Howes, M.-J.R., Houghton, P.J., Barlow, D.J., Pocock, V.J., Milligan, S.R., 2002. Assessment of estrogenic activity in some common essential oil constituents. J. Pharm. Pharmacol. 54 (11), 1521–1528.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Ishida, T., Toyota, M., Asakawa, Y., 1989. Terpenoid biotransformation in mammals -V. metabolism of (+)-citronellal, (+-)-7-hydroxycitronellal, citral, (-)-perillaldehyde, (-)-myrtenal, cuminaldehyde, thujone, and (+-)-carvone in rabbits. Xenobiotica 19 (8), 843–855.

Ishidate Jr., M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Food Chem. Toxicol. 22 (8), 623–636.

Jackson, G.M., Hall, D.E., Walker, R., 1987. Comparison of the short-term hepatic effects of orally administered citral in Long Evans hooded and Wistar albino rats. Food Chem. Toxicol. 25 (7), 505–513.

Kessler, O.J., Keisari, Y., Servadio, C., Abramovici, A., 1998. Role of chronic inflammation in the promotion of prostatic hyperplasia in rats. J. Urol. 159 (3), 1049–1053.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Kuroda, K., Tanaka, S., Yu, Y.S., Ishibashi, T., 1984. Rec-assay of food additives. Nippon Kosnu Eisei Zasshi 31 (6), 277–281.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Leach, E.H., Lloyd, J.P.F., 1956. Experimental ocular hypertension in animals. Trans. Ophthalmol. Soc. UK 76, 453–460.

Lutz, D., Eder, E., Neudecker, T., Henschler, D., 1982. Stucture-mutagenicity relationship in alpha,beta-unsaturated carbonylic compounds and their corresponding allylic

alcohols. Mutat. Res. Fund Mol. Mech. Mutagen 93 (2), 305–315.
Marzulli, F.N., Maibach, H.I., 1980. Contact allergy: predictive testing of fragrance ingredients in humans by Draize and maximization methods. J. Environ. Pathol. Toxicol. 3 (5–6), 235–245.
Ministry of Health and Welfare, 1996. Simplified Reprotoxicity Rat Study on Citral. (Unpublished).
National Toxicology Program, 2003. Toxicology and Carcinogenesis Studies of Citral (Microencapsulated) (CAS No. 5392-40-5) in F344/N Rats and B6C3F1 Mice (Feed Studies). NTP-TR-505. NIH Publication No. 03-4439.
Nogueira, A.C.M.A., Carvalho, R.R., Souza, C.A.M., Chahoud, I., Paumgartten, F.J.R., 1995. Study on the embryofeto-toxicity of citral in the rat. Toxicology 96 (2), 105–113.
Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978. Mutagenicity of food flavours in bacteria (1st Report). Osaka-furitsu Koshu Eisei Kenkyu Hokoku Shokuhin Eisei Hen 9, 177–181.
OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.
Phillips, J.C., Kingsnorth, J., Gangolli, S.D., Gaunt, I.F., 1976. Studies on the absorption, distribution and excretion of citral in the rat and mouse. Food Chem. Toxicol. 14 (6), 537–540.
Ress, N.B., Hailey, J.R., Maronpot, R.R., Bucher, J.R., Travlos, G.S., Haseman, J.K., Orzech, D.P., Johnson, J.D., Hejtmancik, M.R., 2003. Toxicology and carcinogenesis studies of microencapsulated citral in rats and mice. Toxicol. Sci. 71 (2), 198–206.
RIFM (Research Institute for Fragrance Materials, Inc), 1958. Toxicological Screening of Citral and Citral Diethyl Acetal in Rats. Class X. Citral Compounds. Unpublished report from Trubek Laboratories, Inc. RIFM report number 29147. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1977. Capacity for Allergic Sensitization of Citronellal Determined by the Maximization Test on guinea Pigs. Unpublished report from Givaudan. RIFM report number 57064. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1980. Delayed Contact Hypersensitivity Study in guinea Pigs with 5,9-Dimethyl-4,8-Decadienal. Unpublished report from International Flavors and Fragrances. RIFM report number 51129. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1981. Repeated Insult Patch Test with 5,9-Dimethyl-4,8-Decadienal. Unpublished report from International Flavors and Fragrances. RIFM report number 51128. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2006. Partition Coefficient N-Octanol/water of Citral (Citral Lemarome N). Unpublished report from Givaudan. RIFM report number 51398. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008. Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. RIFM report number 55663. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of 5,9-Dimethyl-4,8-Decadienal in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65898. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2014. Citronellal: Repeated Insult Patch Test (RIPT). RIFM report number 68401. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2016. Citral: Prenatal Developmental Toxicity Study in new zealand White Rabbits Oral Administration (Gavage). Unpublished report from RIFM report number 71160. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2016. Exposure Survey, vol. 12 August 2016.
Robinson, M.K., Fletcher, E.R., Johnson, G.R., Wyder, W.E., Maurer, J.K., 1990. Value of the cutaneous basophil hypersensitivity (CBH) response for distinguishing weak contact sensitization from irritation reactions in the Guinea pig. J. Invest. Dermatol. 94 (5), 636–643.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Sandbank, M., Abramovici, A., Wolf, R., David, E.B., 1988. Sebaceous gland hyperplasia following topical application of citral-an ultrastructural study. Am. J. Dermatopathol. 10 (5), 415–418.
Scolnik, M., Konichezky, M., Tykochinsky, G., Servadio, C., Abramovici, A., 1994b. Immediate vasoactive effect of citral on the adolescent rat ventral prostate. Prostate 25 (1), 1–9.
Scolnik, M.D., Servadio, C., Abramovici, A., 1994a. Comparative study of experimentally induced benign and atypical hyperplasia in the ventral prostate of different rat strains. J. Androl. 15 (4), 287–297.
Servadio, C., Abramovici, A., Sandbank, U., Rosen, M., 1986a. Early stages of the pathogenesis of rat ventral prostate hyperplasia induced by citral. Eur. Urol. 12 (3), 195–200.
Servadio, C., Abramovici, A., Sandbank, U., Savion, M., Shmueli, D., 1986b. Further studies on the experimental induction of benign hyperplasia of the prostate in rats by citral. J. Urol. 135 (4 Part 2), 352A.
Servadio, C., Abramovici, A., Schmueli, J., Sandbank, U., 1987. Further observations on citral-induced changes in the ventral prostate of the rat. J. Urol. 137 (4 Part 2), 369A.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Shillinger, Y.I., 1950. Action of some synthetic substances on animals' organism. Gig. Sanit. 3, 37–41.
Toaff, M.E., Abramovici, A., Sporn, J., Liban, E., 1979. Selective oocyte degeneration and impaired fertility in rats treated with the aliphatic monoterpene, citral. J. Reprod. Fertil. 55, 347–352.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. J. Osaka City Med. Cent. 34 (3–4), 267–288 [Osaka-shi Igakkai Zasshi].
Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., 1987. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environ. Mutagen. 9 (S9), 1–110.