Food and Chemical Toxicology 173 (2023) 113560

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal, CAS registry number 17909-77-2

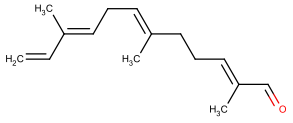
A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], M. Na [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, 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*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, 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*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, 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*

ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

Version: 120522. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



(*continued on next column*)

(*continued*)

Name: 2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal
CAS Registry Number: 17909-77-2

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

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2022.113560
Received 9 December 2022; Accepted 12 December 2022
Available online 16 December 2022

(*continued*)

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

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

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

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

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

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

2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs 3,7-dimethyl-2-methylenocta-6-enal and α-farnesene (CAS # 22418-66-2 and 502-61-4) show that 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog 2-decenal (CAS # 3913-71-1) provided 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal a No Expected Sensitization Induction Level (NESIL) of 230 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra for the read-across analog farnesal (CAS # 19317-11-4); 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; for the hazard assessment based on the screening data, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal was not able to be risk screened as there were no reported volumes of use (VoU) for either North America or Europe in the 2019 IFRA Survey.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2002; RIFM, 2016; RIFM, 2017c; RIFM, 2017b)
Repeated Dose Toxicity: No data available. Exposure is below the TTC.
Reproductive Toxicity: No data available. Exposure is below the TTC.
Skin Sensitization: NESIL = 230 μg/cm^2 (RIFM, 2017a)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.
(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 2.7 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 2329 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Not applicable
Risk Assessment:
- Not applicable; No 2019 IFRA VoU reported

1. Identification

1. **Chemical Name:** 2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal
2. **CAS Registry Number:** 17909-77-2
3. **Synonyms:** 2,6,9,11-Dodecatrienal, 2,6,10-trimethyl-, (E,E,E)-; α-Sinensal; (E,E,E)-2,6,10-Trimethyldodeca-2,6,9,11-tetraen-1-al; 2,6,10-Trimethyldodeca-2,6,9,11-tetraenal; 2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal
4. **Molecular Formula:** $C_{15}H_{22}O$
5. **Molecular Weight:** 218.34 g/mol
6. **RIFM Number:** 5087
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 301.08 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 5.61 (EPI Suite)
4. **Melting Point**: 15.45 °C (EPI Suite)
5. **Water Solubility:** 0.5734 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00112 mm Hg at 20 °C (EPI Suite v4.0), 0.00184 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Not available
9. **Appearance/Organoleptic:** Not available

3. Volume of use (Worldwide band)

1. No volume of use reported in 2019 (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0090% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000012 mg/kg/day or 0.00090 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00012 mg/kg/day (RIFM, 2019)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** 3,7-Dimethyl-2-methylenocta-6-enal and α-farnesene (CAS # 22418-66-2 and 502-61-4)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Read-across: 2-Decenal (CAS # 3913-71-1); Weight of Evidence (WoE): Linoleic acid (CAS # 60-33-3)
   e. **Photoirritation/Photoallergenicity:** Farnesal (CAS # 19317-11-4)
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal is reported to occur in the following foods by the VCF*:

8.1. Citrus fruits

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

9. REACH dossier

2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal has been pre-registered for 2010; no dossier available as of 12/05/22.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.018
2	Products applied to the axillae	0.0053
3	Products applied to the face/body using fingertips	0.11
4	Products related to fine fragrances	0.099
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.025
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.025
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.025
5D	Baby cream, oil, talc	0.025
6	Products with oral and lip exposure	0.058
7	Products applied to the hair with some hand contact	0.20
8	Products with significant ano-genital exposure (tampon)	0.010
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.19
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.69
10B	Aerosol air freshener	0.69
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.38
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal, the basis was a skin sensitization NESIL of 230 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.7.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal; however, read-across can be made to 3,7-dimethyl-2-methylenocta-6-enal and α-farnesene (CAS # 22418-66-2 and 502-61-4; see Section VI).

The mutagenic activity of 3,7-dimethyl-2-methylenocta-6-enal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 3,7-dimethyl-2-methylenocta-6-enal in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2002). Under the conditions of the study, 3,7-dimethyl-2-methylenocta-6-enal was not mutagenic in the Ames test, and this can be extended to 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal.

The mutagenic activity of α-farnesene has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with α-farnesene in dimethylformamide (DMF) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2016). Under the conditions of the study, α-farnesene was not mutagenic in the Ames test, and this can be extended to 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal.

The clastogenic activity of 3,7-dimethyl-2-methylenocta-6-enal was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 3,7-dimethyl-2-methylenocta-6-enal in DMSO at concentrations up to 1660 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 50 μg/mL in the presence and absence of metabolic activation. 3,7-Dimethyl-2-methylenocta-6-enal did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2017). Under the conditions of the study, 3,7-dimethyl-2-methylenocta-6-enal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2,6-dimethyl-10--methylene-2,6,11-dodecatrienal.

The clastogenic activity of α-farnesene was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with α-farnesene in DMF at concentrations up to 1000 μg/mL in the DRF study; micronuclei analysis was conducted at concentrations up to 200 μg/mL in the presence and absence of metabolic activation. α-farnesene did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, α-farnesene was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal.

Based on the data available, 3,7-dimethyl-2-methylenocta-6-enal and α-farnesene do not present a concern for genotoxic potential, and this can be extended to 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/21/22.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal or any read-across materials. The total systemic exposure to 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal (0.12 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/03/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal or any read-across materials. The total systemic exposure to 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal (0.12 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/03/22.

11.1.4. Skin sensitization

Based on read-across material 2-decenal (CAS # 3913-71-1) and WoE material linoleic acid (CAS # 60-33-3), 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal was assigned a NESIL of 230 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

11.1.4.1. Risk assessment. Limited data are available on the skin sensitization potential of 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal. Therefore, structurally related materials, read-across material 2-decenal (CAS # 3913-71-1; see Section VI) and WoE material linoleic acid (CAS # 60-33-3; see Section VI) were used for the risk assessment of 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal. The data on the read-across material are summarized in Table 1. The chemical structure of these materials indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Read-across material 2-decenal was found to be positive in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens, and U-SENS (Natsch, 2013). In murine local lymph node assays (LLNAs), the read-across material 2-decenal and WoE material linoleic acid were found to be sensitizing with EC3 values of 2.5% (625 μg/cm^2) and 14.1% (3525 μg/cm^2), respectively (Roberts et al., 2007; Gerberick et al., 2005; Kreiling et al., 2008). In 2 human maximization tests, no reactions were observed when read-across 2-decenal at 4% (2760 μg/cm^2) in petrolatum was used for induction and challenge (RIFM, 1973a; RIFM, 1977). Additionally, in In 2 Confirmation of No Induction in Humans tests (CNIHs), no reactions indicative of sensitization were observed when read-across material 2-decenal at 0.125% (97 μg/cm^2) in alcohol SDA 39C and 2% (unknown patch size) in dimethyl phthalate was used for induction and challenge in 49 and 53 volunteers, respectively (RIFM, 1973b; RIFM, 1970). In a CNIH conducted according to Politano and Api (Politano, 2008) with 0.2% w/v or 236 μg/cm^2 read-across *trans*-2--decenal in 1:3 ethanol:diethyl phthalate, no reactions indicative of

Table 1
Summary of existing data on 2-decenal as a read-across for 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA Weighted Mean EC3 Value μg/cm^2	GPMT[d]	Buehler[d]
Strong	236	2760	NA	230	625	NA	NA
	***In vitro* Data[e]**				***In silico* protein binding alerts (OECD Toolbox v4.5)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	Positive	Positive	Positive		Michael addition	Michael addition	Michael addition

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

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Studies conducted according to the OECD TG 406 are included in the table.

[e] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

sensitization were observed in any of the 105 volunteers (RIFM, 2017a).

Based on WoE from structural analysis and *in vitro*, animal, and human studies on the read-across material, the WoE material, and the target material, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal was assigned a WoE NESIL of 230 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020).

Additional References: Natsch (2007), Natsch (2008), McKim et al., 2010.

Literature Search and Risk Assessment Completed On: 01/21/22.

11.1.5. Photoirritation/photoallergenicity

Based on the UV/Vis absorption spectra for the structurally related material farnesal (CAS # 19317-11-4; see Section VI) 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal in experimental models. UV/Vis absorption spectra are not available for the target material, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal. UV/Vis absorbance spectra for the structurally related material farnesal (CAS # 19317-11-4) indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance for the structurally related analog, 2, 6-dimethyl-10-methylene-2,6,11-dodecatrienal does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra were not available for the target material 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal. UV/Vis absorbance spectra for the structurally related material farnesal (CAS # 19317-11-4) indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/18/22.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal. Based on the Creme RIFM Model, the inhalation exposure is 0.00090 mg/day. This exposure is 1556 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: 01/17/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal was not assessed as no volume of use was reported.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal as not possibly persistent but bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI

Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Not applicable.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.3. Ecotoxicity. No data available.

11.2.1.4. Other available data. 2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal has been pre-registered for REACH with no additional data at this time.

11.2.1.5. Risk assessment refinement. Not applicable; no 2019 IFRA VoU reported.

Literature Search and Risk Assessment Completed On: 07/05/22.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
  - **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
  - **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
  - **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
  - **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
  - **IARC:** https://monographs.iarc.fr
  - **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
  - **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
  - **US EPA ChemView:** https://chemview.epa.gov/chemview/
  - **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
  - **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://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 12/05/22.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113560.

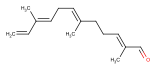
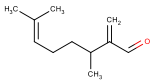
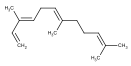
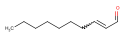
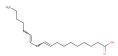
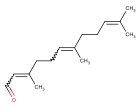
Appendix

Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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 v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material	WoE Material	Read-across Material
Principal Name	2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal	3,7-Dimethyl-2-methylenocta-6-enal	α-Farnesene	2-Decenal	Linoleic acid	Farnesal
CAS No.	17909-77-2	22418-66-2	502-61-4	3913-71-1	60-33-3	19317-11-4
Structure						
Similarity (Tanimoto Score)		0.39	0.80	0.39	0.34	0.70
Endpoint		Genotoxicity	Genotoxicity	Skin sensitization	Skin sensitization	Photoirritation/photoallergenicity
Molecular Formula	$C_{15}H_{22}O$	$C_{11}H_{18}O$	$C_{15}H_{24}$	$C_{10}H_{18}O$	$C_{18}H_{32}O_2$	$C_{15}H_{24}O$
Molecular Weight (g/mol)	218.34	166.26	204.36	154.25	280.45	220.36
Melting Point (°C, EPI Suite)	15.45	−26.86	−17.22	−8.92	−6.90	16.65
Boiling Point (°C, EPI Suite)	301.08	217.71	261.11	230.00	389.19	302.17
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.25	19.60	3.33	10.43	0.00	0.23
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.57	27.56	0.01	67.82	1.59	0.43
Log K_{OW}	5.61	3.94	7.10	3.55	7.05	5.74
J_{max} (μg/cm^2/h, SAM)	0.09	3.89	0.00	8.68	0.24	0.07
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	98.99	42.86	267498.00	31.11	0.02	163.13
Genotoxicity						
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	AN2|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds ≫ α,β-Unsaturated Aldehydes|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ α,β-Unsaturated Aldehydes	AN2|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds ≫ α,β-Unsaturated Aldehydes|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ α,β-Unsaturated Aldehydes	No alert found			
DNA Binding (OECD QSAR Toolbox v4.5)	Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition ≫ α,β- unsaturated aldehydes	Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition ≫ α,β- unsaturated aldehydes	No alert found			
Carcinogenicity (ISS)	α,β-unsaturated carbonyls (Genotox)|Structural alert for genotoxic carcinogenicity	α,β-unsaturated carbonyls (Genotox)|Structural alert for genotoxic carcinogenicity	No alert found			
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found			
***In Vitro* Mutagenicity (Ames, ISS)**	α,β-unsaturated carbonyls	α,β-unsaturated carbonyls	No alert found			
***In Vivo* Mutagenicity (Micronucleus, ISS)**	Alert for Schiff base formation identified.	Alert for Michael Acceptor identified.	No skin sensitization reactivity domains alerts identified.			
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds	Not classified			
Skin Sensitization						
Protein Binding (OASIS v1.1)	Michael addition|Michael addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds|Michael			Michael addition|Michael addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds|	No alert found	

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	WoE Material	Read-across Material
	addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds ≫ α,β-Aldehydes |Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes			Michael addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds ≫ α,β-Aldehydes |Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds| Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes		
Protein Binding (OECD)	Michael addition|Michael addition ≫ Polarised Alkenes|Michael addition ≫ Polarised Alkenes ≫ Polarised alkene - aldehydes|Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls			Michael addition| Michael addition ≫ Polarised Alkenes| Michael addition ≫ Polarised Alkenes ≫ Polarised alkene - aldehydes|Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers| Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	No alert found	
Protein Binding Potency	Moderately reactive (GSH)| Moderately reactive (GSH) ≫ Substituted 2-Alken-1-als (MA)			Highly reactive (GSH)| Highly reactive (GSH) ≫ 2-Alken-1-als (MA)	Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Michael Addition|Michael Addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds|Michael Addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds ≫ α,β-Aldehydes			Michael Addition| Michael Addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds| Michael Addition ≫ Michael addition on α,β-Unsaturated carbonyl compounds ≫ α,β-Aldehydes	No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.			Alert for Michael Acceptor identified.	No skin sensitization reactivity domains alerts identified.	
Metabolism						
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5	See Supplemental Data 6

Summary

There are insufficient toxicity data on 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal (CAS # 17909-77-2). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 3,7-dimethyl-2-methylenocta-6-enal (CAS # 22418-66-2), α-farnesene (CAS # 502-61-4), 2-decenal (CAS # 3913-71-1), linoleic acid (CAS # 60-33-3), and farnesal (CAS # 19317-11-4) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 3,7-Dimethyl-2-methylenocta-6-enal (CAS # 22418-66-2) was used as a read-across analog for the target material, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal (CAS # 17909-77-2), for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to the class of unsaturated aliphatic aldehydes.
  - o The key difference between the target and the read-across analog is that the target material is a C12 aldehyde with 3 vinylene moieties and a vinyl moiety, whereas the read-across analog is a C8 aldehyde with a vinylene moiety and a vinyl moiety. Moreover, there is vinylene-vinyl conjugation in the target material, which is lacking in the read-across analog. Also, the target material has a bis-allylic carbon which is again lacking in the read-across analog. The presence of an α,β-unsaturated aldehyde in both the target material and the read-across analog makes

them equally reactive towards the dominant mode of action, which is a Michael addition.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score.
  - According to the OECD QSAR Toolbox v4.5, the structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and the read-across analog have an alert for a Michael addition. This is due to the α, β-unsaturated aldehyde. An initial Michael addition mechanism has been suggested to be primarily responsible for the ability of these chemicals to alkylate DNA. In addition, there is also an alert for AN2-based Schiff base formation for both the target material and the read-across analog. This alert is due to the presence of the α,β-unsaturated aldehyde. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genotoxicity. Therefore, based on structural similarity and data for the read-across analog, the alert is superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- α-Farnesene (CAS # 502-61-4) was used as a read-across analog for the target material, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal (CAS # 17909-77-2) for the genotoxicity endpoint.
  - The target material belongs to the class of aldehydes, whereas the read-across analog belongs to the class of alkenes.
  - Both the target material and the read-across analog share 2 structural features: a vinyl-vinylene conjugation and a bis-allylic carbon.
  - The key difference between the target and the read-across analog is that the target material is a C12 aldehyde with 3 vinylenes moieties and a vinyl moiety, whereas the read-across analog is a C12 alkene with 3 methyl substituents. The read-across analog covers the structural features, vinyl-vinylene conjugation, and a bis-allylic carbon of the target material.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score.
  - According to the OECD QSAR Toolbox v4.5, the structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material has an alert for a Michael addition. This is due to the α, β-unsaturated aldehyde. An initial Michael addition mechanism has been suggested to be primarily responsible for the ability of such chemicals to alkylate DNA. In addition, there is also an alert for AN2-based Schiff base formation for the target material. This alert is due to the presence of the α, β-unsaturated aldehyde. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genotoxicity. Therefore, based on structural similarity and data for the read-across analog, the alert is superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-Decenal (CAS # 3913-71-1) was used as a read-across analog for the target material, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal (CAS # 17909-77-2), for the skin sensitization endpoint.
  - The target material and the read-across analog belong to the class of a,b-unsaturated aldehydes.
  - The key difference between the target and the read-across analog is that the target material is a C12 aldehyde with 3 vinylenes moieties and a vinyl moiety, whereas the read-across analog is a C10 aldehyde with a vinylene moiety. Moreover, there is vinylene-vinyl conjugation in the target material, which is lacking in the read-across analog. Also, the target material has a bis-allylic carbon which is again lacking in the read-across analog. The presence of the α,β-unsaturated aldehyde in both the target material and the read-across analog makes them equally reactive towards the dominant mode of action, which is a Michael addition.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score.
  - According to the OECD QSAR Toolbox v4.5, the structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and the read-across analog have an alert for a Michael addition. This is due to the α, β-unsaturated aldehyde. An initial Michael addition mechanism has been suggested to be primarily responsible for the ability of these chemicals to alkylate DNA. In addition, there is also an alert for AN2-based Schiff base formation for both the target material and the read-across analog. This alert is due to the presence of the α,β-unsaturated aldehyde. The data described in the skin section show that the read-across analog does not pose a concern for skin sensitization. Therefore, based on structural similarity and data for the read-across analog, the alert is superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Linoleic acid (CAS # 60-33-3) was used as a WoE analog for the target material, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal (CAS # 17909-77-2), for the skin sensitization endpoint.
  - The target material belongs to the class of unsaturated aldehydes, whereas the WoE analog belongs to the class of unsaturated carboxylic acids.
  - Both the target material and WoE analog share a bis-allylic carbon.
  - The key difference between the target and the WoE analog is that the target material is a C12 aldehyde with 3 vinylenes moieties and a vinyl moiety, whereas the WoE analog is a C18 carboxylic acid with 2 vinylenes. There is vinylene-vinyl conjugation in the target material, which is lacking in the WoE analog. The WoE analog covers the secondary structural feature, the bis-allylic carbon of the target material.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score.
  - According to the OECD QSAR Toolbox v4.5, the structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material has an alert for a Michael addition. This is due to the α, β-unsaturated aldehyde. An initial Michael addition mechanism has been suggested to be primarily responsible for the ability of such chemicals to alkylate DNA. In addition, there is also an alert for AN2-based Schiff base formation for the target material. This alert is due to the presence of the α, β-unsaturated aldehyde. The data described in the skin section show that the WoE analog does not pose a concern for skin sensitization. Therefore, based on structural similarity and data for the WoE analog, the alert is superseded by the data.
  - The target material and the WoE analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the WoE analog and the target material.
- Farnesal (CAS # 19317-11-4) was used as a read-across analog for the target material, 2,6-dimethyl-10-methylene-2,6,11-dodecatrienal (CAS # 17909-77-2), for the photoirritation/photoallergenicity endpoint.
  - The target material and the read-across analog belong to the class of α,β-unsaturated aldehydes.

- The key difference between the target and the read-across analog is that the target material is a C12 aldehyde with 3 vinylenes moieties and a vinyl moiety, whereas the read-across analog is a C12 aldehyde with 3 vinylene moieties. Moreover, there is an α methyl substituent in the target material while there is a β-methyl substituent in the read-across analog. Moreover, there is vinylene-vinyl conjugation in the target material, which is lacking in the read-across analog. This structural difference does not alter the chromophore and light-absorbing properties of the molecule.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score.
- According to the OECD QSAR Toolbox v4.5, the structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog do not have a chromophore that is expected to absorb in the UV/Vis range of the electromagnetic spectrum that is of interest to human health toxicity. The data on the read-across analog confirm that the substance does not absorb in the UV/Vis range. Therefore, the structural difference between the target material and the read-across analog is toxicologically insignificant for the photoirritation/photoallergenicity endpoint, and the target material can be predicted to not absorb in the UV/Vis range.

References

Api, A.M., Basketter, D., Bridges, J., Cadby, P., et al., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 2020, 118, 104805.

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.

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.

Cottrez, F., Boitel, E., Ourlin, J.C., Peiffer, J.L., et al., 2016. A 3D reconstituted epidermis-based model for quantifying chemical sensitization potency: reproducibility and predictivity results from an inter-laboratory study. Toxicol. Vitro 32, 248–260. Apr;.

Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718, 2020.

ECHA, 2017a. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017b. Read-across Assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

Forreryd, A., Zeller, K.S., Lindberg, T., Johansson, H., Linstedt, M., 2016. From genome-wide arrays to tailor-made biomarker readout - progress towards routine analysis of skin sensitizing chemicals with GARD. Toxicol. Vitro 37, 178–188.

Gerberick, G.F., Ryan, C.A., Kern, P.S., Schlatter, H., Dearman, R.J., Kimber, I., Patlewicz, G.Y., Basketter, D.A., 2005. Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods. Dermatitis 16 (4), 157–202.

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.

IFRA (International Fragrance Association), 2019. Volume of Use Survey, January-December 2019.

Kreiling, R., Hollnagel, H.M., Hareng, L., Eigler, D., Lee, M.S., 2008. Comparison of the skin sensitizing potential of unsaturated compounds as assessed by the Murine Local Lymph Node Assay (LLNA) and the Guinea pig maximization test (GPMT). Food Chem. Toxicol. 46 (6), 1896–1904.

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.

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.

McKim Jr., J.M., Keller III, D.J., Gorski, J.R., 2010. A new in vitro method for identifying chemical sensitizers combining peptide binding with ARE/EpRE-medicated gene expression in human skin cells. Cutan. Ocul. Toxicol. 29 (3), 171–192.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

Natsch, A., Gfeller, H., 2008. LC-MS-Based characterization of the peptide reactivity of chemicals to improve the in vitro prediction of the skin sensitization potential. Toxicol. Sci. 106 (2), 464–478.

Natsch, A., Gfeller, H., Rothaupt, M., Ellis, G., 2007. Utility and limitations of a peptide reactivity assay to predict fragrance allergens in vitro. Toxicol. Vitro 21 (7), 1220–1226.

Natsch, A., Ryan, C.A., Foertsch, L., Emter, R., Jaworska, J., Gerberick, F., Kern, P., 2013. A dataset on 145 chemicals tested in alternative assays for skin sensitization undergoing prevalidation. J. Appl. Toxicol. 33 (11), 1337–1352.

OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2021. The OECD QSAR Toolbox, v3.2–4.5. Retrieved from. http://www.qsartoolbox.org/.

Politano, V.T., Api, A.M., 2008. The Research Institute of Fragrance Materials' human repeated insult patch test protocol. Regul. Toxicol. Pharmacol. 52 (1), 35–38.

RIFM (Research Institute for Fragrance Materials, Inc), 1970. Sensitization and Irritation Studies of Fragrance Materials. Unpublished Report from Givaudan-Roure Corporation. RIFM report number 27952. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1973a. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1802. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1973b. Repeated Insult Patch Test with 2-decenal. Unpublished Report from International Flavors and Fragrances. RIFM report number 50625. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1977. Human Maximization Studies. Report to RIFM. RIFM report number 1979. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2002. Reverse Mutation Assay "Ames Test" Using Salmonella typhimurium and Escherichia coli with 3,7-Dimethyl-2-Methylenocta-6-Enal. Unpublished Report from IFF. RIFM report number 48826. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of 2,6-Dimethyl-10-Methylene-2,6,11-Dodecatrienal in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65899. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016. Alpha-Farnesene (Farnesene, Mixture of Isomers): Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM report number 69865. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2017a. trans-2-Decenal: Repeated Insult Patch Test. RIFM report number 72571. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2017b. Alpha-Farnesene: in Vitro Human Lymphocyte Micronucleus Assay. RIFM report number 72856. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2017. 3,7-Dimethyl-2-methylenocta-6-enal: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM report number 72926. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2019. Exposure Survey 23. January 2019.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

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.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Thakkar, Y., Joshi, K., Hickey, C., Wahler, J., et al., 2022. The BlueScreen HC assay to predict the genotoxic potential of fragrance materials. Mutagenesis 37 (1), 13–23, 2022.
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, v2.0. United States Environmental Protection Agency, Washington, DC, USA.