Food and Chemical Toxicology 161 (2022) 112919

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, 4,7-decadienal, CAS registry number 934534-30-2

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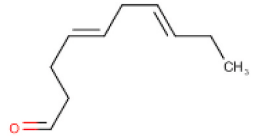
ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 092821. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: 4,7-Decadienal
CAS Registry Number: 934534-30-2
Additional CAS*



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22644-09-3
4,7-Decadienal, (4Z,7Z)- (No Reported Use)
*Included because the materials are isomers

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

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https://doi.org/10.1016/j.fct.2022.112919
Received 30 September 2021; Received in revised form 11 January 2022; Accepted 8 March 2022
Available online 11 March 2022

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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.

4,7-Decadienal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4,7-decadienal is not 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 4,7-decadienal 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 10-undecenal (CAS # 112-45-8) provided 4,7-decadienal a No Expected Sensitization Induction Level (NESIL) of 1700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 4,7-decadienal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4,7-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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2020c; RIFM, 2019; RIFM, 2021)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: NESIL = 1700 μg/cm^2.	RIFM (2016)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/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: 3.18 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 73.46 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 14.30 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 14.30 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.01430 μg/L	

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe (No VoU): Not applicable; cleared at screening-level

1. Identification

1. Chemical Name: 4,7-Decadienal	1. Chemical Name: 4,7-Decadienal, (4Z,7Z)-
2. CAS Registry Number: 934534-30-2	**2. CAS Registry Number:** 22644-09-3
3. Synonyms: Tanzinal 10% TEC; 4,7-Decadienal	**3. Synonyms:** 4,7-Decadienal, (4Z,7Z)-
4. Molecular Formula: $C_{10}H_{16}O$	**4. Molecular Formula:** $C_{10}H_{16}O$
5. Molecular Weight: 152.23 g/mol	**5. Molecular Weight:** 152.23 g/mol
6. RIFM Number: 323	**7. RIFM Number:** 323
8. Stereochemistry: Isomer not specified. Two stereocenters available and 4 total stereoisomers possible.	**8. Stereochemistry:** 4Z, 7Z isomer specified.

2. Physical data

1. Boiling Point: 227.73 °C (EPI Suite)	1. Boiling Point: Not Available
2. Flash Point: Not Available	**2. Flash Point:** Not Available
3. Log K_{OW}: 3.33	**3. Log K_{OW}:** Not Available
4. Melting Point: −9.78 °C (EPI Suite)	**4. Melting Point**: Not Available
5. Water Solubility: 1.06E+02 mg/L at 25 °C (WSKOW v1.42 in EPI Suite)	**5. Water Solubility:** Not Available
6. Specific Gravity: Not Available	**6. Specific Gravity:** Not Available
7. Vapor Pressure: 1.17E+01 Pa at 25 °C (EPI Suite)	**7. Vapor Pressure:** Not Available

(*continued on next page*)

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8. UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**8. UV Spectra:** Not Available
9. Appearance/Organoleptic: Not Available	**9. Appearance/ Organoleptic:** Not Available

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.000023% (RIFM, 2017b)
2. **Inhalation Exposure**:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2017b)
3. **Total Systemic Exposure***: 0.0000003 mg/kg/day (RIFM, 2017b)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrances or 95th percentile, inhalation exposure, and total exposure.

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

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford, 2015, 2017; and Comiskey et al., 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 v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 10-Undecenal (CAS # 112-45-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References:

None.

8. Natural occurrence

4,7-Decadienal is not reported to occur in foods by the VCF*.

4,7-Decadienal, (4Z,7Z)- is reported to occur in the following foods by the VCF:

Calamus (sweet flag) (*Acorus calamus* L.)

*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

Neither 4,7-decadienal or 4,7-decadienal, (4Z,7Z)- are pre-registered; no dossiers available as of 09/28/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 4,7-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)	0.13
2	Products applied to the axillae	0.039
3	Products applied to the face/body using fingertips	0.78
4	Products related to fine fragrances	0.73
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.18
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.18
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.18
5D	Baby cream, oil, talc	0.18
6	Products with oral and lip exposure	0.43
7	Products applied to the hair with some hand contact	1.5
8	Products with significant ano-genital exposure (tampon)	0.077
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	5.1
10B	Aerosol air freshener	5.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	2.8
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 4,7-decadienal, the basis was a skin sensitization NESIL of 1700 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).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 4,7-decadienal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 4,7-decadienal 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 4,7-decadienal 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, 2020c). Under the conditions of the study, 4,7-decadienal was not mutagenic in the Ames test.

The clastogenic activity of 4,7-decadienal 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 4,7-decadienal in DMSO at concentrations up to 5000 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1600 μg/mL in the presence and absence of metabolic activation. 4,7-Decadienal did induce a statistically significant and dose-dependent increase in binucleated cells with micronuclei (1.20%), which was outside the historical 95% control limit of 0.06%–0.54% when tested up to the cytotoxic level concentration in the 4-h treatment in the presence of an S9 activation system (RIFM, 2019). Under the conditions of the study, 4,7-decadienal was considered to be clastogenic in the *in vitro* micronucleus test.

To confirm the positive results seen in the *in vitro* micronucleus assay, a statistically significant and dose-dependent increase in micronucleus test, a more biologically relevant assay was performed. A GLP-compliant 3D reconstructed skin micronucleus (RSMN) assay was conducted to evaluate the genotoxic potential of 4,7-decadienal (CAS # 934534-30-2) in EpiDerm. Acetone was used as the vehicle. EpiDerm tissues were treated with 4,7-decadienal at 24-h intervals for 48 and 72 h, at concentrations up to 100 mg/mL 4,7-decadienal did not induce binucleated cells with micronuclei when tested up to the cytotoxic level or the maximum concentration (RIFM, 2021). Under the conditions of the study, 4,7-decadienal was concluded to be negative for the induction of micronuclei in the RSMN in EpiDerm. As an additional weight of evidence there is an *in vivo* micronucleus study which was also concluded to be negative (RIFM, 2017a).

In addition, the total chronic systematic exposure of 4,7-decadienal is 0.0003 μg/kg/day, which is below the genotoxicity threshold for toxicological concern of 0.0025 μg/kg/day (Kroes et al., 2004). Based on the data and exposure information available, 4,7-decadienal does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/06/20.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 4,7-decadienal or any read-across materials. The total systemic exposure to 4,7-decadienal 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 no repeated dose toxicity data on 4,7-decadienal or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.0003 μg/kg/day) is below the TTC for 4,7-decadienal (30 μg/kg/day; Kroes et al., 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/15/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 4,7-decadienal or any read-across materials. The total systemic exposure to 4,7-decadienal 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 no reproductive toxicity data on 4,7-decadienal or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.0003 μg/kg/day) is below the TTC for 4,7-decadienal (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

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

11.1.4. Skin sensitization

Based on read-across material 10-undecenal (CAS # 112-45-8), 4,7-decadienal is considered a skin sensitizer with a defined NESIL of 1700 μg/cm^2.

11.1.4.1. Risk assessment. No skin sensitization studies are available for 4,7-decadienal. Based on read-across material 10-undecenal (CAS # 112-45-8; see Section VI), 4,7-decadienal is considered a skin sensitizer. The chemical structure of these materials indicate that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Contrary to the *in silico* prediction, 10-undecenal was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and human cell line activation test (h-CLAT) but positive in the KeratinoSens assay (Urbisch, 2015). In a murine local lymph node assay (LLNA), read-across material 10-undecenal was tested at 5%, 10%, 25%, 50%, and 75% and found to be sensitizing with an EC3 value of 6.8% (1700 μg/cm^2) (Patlewicz et al., 2003; Roberts et al., 2007; Gerberick et al., 2005). However, in another LLNA, no skin sensitization reactions were observed when 10-undecenal was tested at 1%, 2.5%, 5%, 10%, and 25% (RIFM, 2001). In both LLNA studies, 4:1 acetone:olive oil was used as a vehicle. In guinea pig tests, including open epicutaneous tests, a Draize test, a guinea pig maximization test, and a Freund's complete adjuvant test, read-across material 10-undecenal did not present reactions indicative of sensitization (Klecak et al., 1977; Klecak, 1979, 1985). While the conclusions of the guinea pig tests were reported as negative, limited experimental details were available on these studies. In human maximization studies on 25 subjects, no reactions indicative of sensitization were observed with up to 3450 μg/cm^2 of read-across material 10-undecenal (RIFM, 1971; RIFM, 1977). Moreover, in confirmatory Confirmation of No Induction in Humans tests (CNIHs), read-across material 10-undecenal did not induce sensitization reactions at the maximum tested level of 1.5% or 1772 μg/cm^2 in 115 subjects (RIFM, 2016; RIFM, 1964).

Based on the weight of evidence (WoE) from structural analysis and data on the read-across material 10-undecenal, 4,7-decadienal is a sensitizer with a WoE NESIL of 1700 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. (RIFM, 2020b).

Additional References: ECHA, 2013.

Literature Search and Risk Assessment Completed On: 10/21/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 4,7-decadienal would not be

Table 1
Data summary for 10-undecenal as read-across material for 4,7-decadienal.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Sensitization Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
1700 [1]	Moderate	1772	3450	NA	1700

NOEL = No observed effect level; LOEL = lowest observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; NA = Not Available.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 4,7-decadienal in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 4,7-decadienal does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/23/20.

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 4,7-decadienal 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 4,7-decadienal. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 14000 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: 11/05/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4,7-decadienal was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 4,7-decadienal was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 4,7-decadienal as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 4,7-decadienal presents no risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.3.3. Other available data. 4,7-Decadienal has not been registered for REACH at this time.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.33	3.33
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	No VoU	<1
Risk Characterization: PEC/PNEC	**NA**	**<1**

*Combined Regional Volumes of Use for both CAS #s.

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

The RIFM PNEC is 0.01430 μg/L. The revised PEC/PNECs for EU (No

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	14.30			1000000	0.01430	

VoU) and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 10/21/20.

12. Literature Search*

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

Search keywords: CAS number and/or material names.

*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 09/28/21.

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.2022.112919.

Appendix

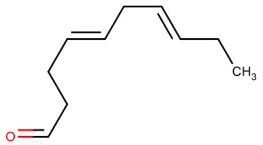
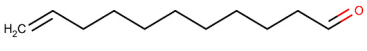
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow 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, 2017).

- 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 v4.11 (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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).

- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	4,7-Decadienal	10-Undecenal
CAS No.	934534-30-2	112-45-8
Structure		
Similarity (Tanimoto Score)		0.36
Endpoint		Skin sensitization
Molecular Formula	$C_{10}H_{16}O$	$C_{11}H_{20}O$
Molecular Weight (g/mol)	152.23	168.28
Melting Point (°C, EPI Suite)	−9.78	1.73
Boiling Point (°C, EPI Suite)	227.73	233.44
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.17E+01	8.71E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.06E+02	1.91E+01
Log K_{OW}	3.33	4.12
J_{max} (μg/cm^2/h, SAM)	11.79	2.88
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.13E+01	6.56E+01
Skin Sensitization		
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ 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)	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.	Alert for Schiff base formation identified.
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on 4,7-decadienal (CAS # 934534-30-2). 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, 10-undecenal (CAS # 112-45-8) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 10-Undecenal (CAS # 112-45-8) was used as a read-across analog for the target material 4,7-decadienal (CAS # 934534-30-2) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of aliphatic aldehydes.
  - o The target material and the read-across analog share an aldehyde functional group.
  - o The key difference between the target material and the read-across analog is that the target material has 2 vinylene bonds, whereas the read-across analog has 1 vinyl bond. The read-across analog contains the structural features of the target material that are relevant to the skin sensitization endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.

- o The target material and the read-across analog have alerts for Schiff base formation by various models for skin sensitization. The read-across analog data confirms that the substance does not pose a concern towards skin sensitization under the current exposure. Therefore, based on the structural similarity between the target material and the read-across analog, and the data for the read-across analog, the *in silico* predictions are superseded by the data.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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