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RIFM fragrance ingredient safety assessment, 2-*trans*-6-*cis*-dodecadienal, CAS Registry Number 21662-13-5

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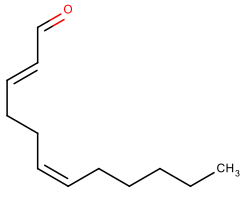

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Name: 2-*trans*-6-*cis*-Dodecadienal CAS Registry Number: 21662-13-5

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

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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., 2020)
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; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use, but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

*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-*trans*-6-*cis*-Dodecadienal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the read-across analog nona-2-*trans*-6-*cis*-dienal (CAS # 557-48-2) show that 2-*trans*-6-*cis*-dodecadienal 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-*trans*-6-*cis*-dodecadienal is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analogs 2-decenal (CAS # 3913-71-1) and *trans*-2-decenal (CAS # 3913-81-3) provided 2-*trans*-6-*cis*-dodecadienal a No Expected Sensitization Induction Level (NESIL) of 230 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-*trans*-6-*cis*-dodecadienal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-*trans*-6-*cis*-dodecadienal 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 expected to be genotoxic. (RIFM, 2017a; RIFM, 2015)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 230 μg/cm^2. RIFM (2017b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 3.12 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 326.7 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 2.33 mg/L (RIFM Framework; Salvito, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 2.33 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.00233 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 2-*trans*-6-*cis*-Dodecadienal
2. **CAS Registry Number:** 21662-13-5
3. **Synonyms:** 2,6-Dodecadienal, (E,Z)-; Dodeca-2,6-dienal; 2-*trans*-6-*cis*-Dodecadienal
4. **Molecular Formula:** $C_{12}H_{20}O$
5. **Molecular Weight:** 180.29
6. **RIFM Number:** 1244
7. **Stereochemistry:** 2E, 6Z or 2-*trans*-6-*cis* isomer specified. Two stereocenters and 4 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 130 °C @ 5 mm Hg (FMA), 263.14 °C (EPI Suite)
2. **Flash Point:** 210 °F; CC (FMA)
3. **Log K_{OW}:** 4.32 (EPI Suite)
4. **Melting Point**: 11.83 °C (EPI Suite)
5. **Water Solubility:** 11.33 mg/L (EPI Suite)
6. **Specific Gravity:** 0.86 (FMA)
7. **Vapor Pressure:** 0.0134 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
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 Hydroalcoholics:** 0.00021% (RIFM, 2017c)
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or 0.000016 mg/day (RIFM, 2017c)
3. **Total Systemic Exposure**:** 0.0000039 mg/kg/day (RIFM, 2017c)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 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 et al., 2015; Safford et al., 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

6.1. Cramer Classification

Class I, Low.

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

6.2. Analogs selected

a. **Genotoxicity:** Nona-2-*trans*-6-*cis*-dienal (CAS # 557-48-2)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 2-Decenal (CAS # 3913-71-1) and *trans*-2-decenal (CAS # 3913-81-3)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional references

None.

8. Natural occurrence

2-*trans*-6-*cis*-Dodecadienal is reported to occur in the following foods by the VCF*:

Cardamom (*Ellettaria cardamomum* Maton.)
Chicken.
Citrus fruits.
Guinea hen.

*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-*trans*-6-*cis*-Dodecadienal has been pre-registered for 2010; no dossier available as of 05/18/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-*trans*-6-*cis*-dodecadienal is 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	Not restricted

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-*trans*-6-*cis*-dodecadienal, the basis was the 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).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-*trans*-6-*cis*-dodecadienal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic activity of 2-*trans*-6-*cis*-dodecadienal; however, read-across can be made to nona-2-*trans*-6-*cis*-dienal (CAS # 557-48-2; see Section VI).

The mutagenic activity of nona-2-trans-6-cis-dienal has been evaluated in a bacterial reverse mutation assay in *Salmonella typhimurium* strain TA100 and found to be not mutagenic (Eder et al., 1992), and this can be extended to 2-*trans*-6-*cis*-dodecadienal.

To further confirm the results found in the single strain Ames test, an *in vivo* comet assay was conducted in compliance with GLP regulations. The test material was administered in corn oil via oral gavage to groups of male Han Wistar rats (6/sex/dose). Doses of 175, 350, or 700 mg/kg were administered. Rats from each dose level were euthanized at the end of the study, and liver tissue was analyzed for DNA damage (tail intensity and tail moment) in the comet assay. No increases in the group mean tail intensity and tail moment values were observed when compared to the vehicle control group (RIFM, 2015). Under the conditions of the study, nona-2-*trans*-6-*cis*-dienal was considered to be non-mutagenic in the comet assay *in vivo*, and this can be extended to 2-*trans*-6-*cis*-dodecadienal.

There are no data assessing the clastogenic activity of 2-*trans*-6-*cis*-dodecadienal; however, read-across can be made to nona-2-*trans*-6-*cis*-dienal (CAS # 557-48-2; see Section VI). The clastogenic activity of nona-2-*trans*-6-*cis*-dienal was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and equivalent with OECD TG 487. Human peripheral blood lymphocytes were treated with nona-2-*trans*-6-*cis*-dienal in dimethyl sulfoxide at concentrations up to 60 μg/mL in the presence and absence of metabolic activation (S9) at the 4-h and 24-h timepoints. Nona-2-*trans*-6-*cis*-dienal induced increases in binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems at all time points (RIFM, 2017a). Under the conditions of the study, nona-2-*trans*-6-*cis*-dienal was considered to be clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-*trans*-6-*cis*-dodecadienal.

To confirm the results of the *in vitro* micronucleus test, the clastogenic activity of nona-2-*trans*-6-*cis*-dienal was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female Han Wistar mice (6/sex/dose). Doses of 175, 350, or 500 mg/kg were administered. Mice from each dose level were euthanized at 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes (PCEs). The test material did not induce statistically significant increases in the incidence of micronucleated PCEs in the bone marrow (RIFM, 2015). Under the conditions of the study, nona-2-*trans*-6-*cis*-dienal was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to 2-*trans*-6-*cis*-dodecadienal.

Based on the data available, nona-2-*trans*-6-*cis*-dienal does not present a concern for genotoxic potential, and this can be extended to 2-*trans*-6-*cis*-dodecadienal.

11.1.1.2. Additional references. Eder et al., 1992; Eder et al., 1993; Dittberner et al., 1995; Glaab et al., 2001; Eder et al., 1994.

11.1.1.3. Literature search and risk assessment completed on. 04/28/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-*trans*-6-*cis*-dodecadienal or any read-across materials. The total systemic exposure to 2-*trans*-6-*cis*-dodecadienal 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 2-*trans*-6-*cis*-dodecadienal or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.0039 μg/kg/day) is below the TTC for 2-*trans*-6-*cis*-dodecadienal (30 μg/kg bw/day; Kroes et al., 2007).

11.1.2.2. Additional references. None.

11.1.2.3. Literature search and risk assessment completed on. 04/29/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2-*trans*-6-*cis*-dodecadienal or any read-across materials. The total systemic exposure to 2-*trans*-6-*cis*-dodecadienal 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 2-*trans*-6-*cis*-dodecadienal or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.0039 μg/kg/day) is below the TTC for 2-*trans*-6-*cis*-dodecadienal (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

11.1.3.2. Additional references. None.

11.1.3.3. Literature search and risk assessment completed on. 05/07/21.

11.1.4. Skin sensitization

Based on the read-across materials 2-decenal (CAS # 3913-71-1) and *trans*-2-decenal (CAS # 3913-81-3), 2-*trans*-6-*cis*-dodecadienal is a skin sensitizer with a defined NESIL of 230 μg/cm^2.

11.1.4.1. Risk assessment. No data skin sensitization studies are available for the target material, 2-*trans*-6-*cis*-dodecadienal. Based on the read-across materials 2-decenal and *trans*-2-decenal (CAS # 3913-71-1 and CAS # 3913-81-3; see Section VI), the target material is considered a skin sensitizer. The chemical structure of these materials indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.3). The read-across material, *trans*-2-decenal, was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, and U937-CD86 test (Natsch, 2013). In a murine local lymph node assay (LLNA), the read-across material 2-decenal was found to be sensitizing with an EC_3 value of 2.5% (625 μg/cm^2) (Roberts et al., 2007; Gerberick et al., 2005). In 2 separate human maximization tests, no reactions were observed when 2-decenal at 4% or 2760 μg/cm^2 in petrolatum was used for induction and challenge (RIFM, 1977a; RIFM, 1977b). In a Confirmation of No Induction in Humans (HRIPT), no reactions indicative of sensitization were observed when 2-decenal at 0.125% in alcohol SDA 39C (97 μg/cm^2) was used for induction and challenge (RIFM, 1973). The dose per unit area could not be calculated because the patch size was not specified for this study. In another CNIH conducted with 0.2% w/v (236 μg/cm^2) *trans*-2-decenal in 1:3 ethanol:diethy phthalate, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2017b).

Based on weight of evidence (WoE) from structural analysis and data on the read-across materials, 2-*trans*-6-*cis*-dodecadienal is a sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 230 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account

Table 1
Data Summary for 2-decenal and *trans*-2-decenal as read-across material for 2-*trans*-6-*cis*-dodecadienal.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-HRIPT (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[2] (Induction) μg/cm^2	WoE NESIL[3] μg/cm^2
625 [1]	Moderate	236	2760	N/A	230

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

skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020).

11.1.4.2. Additional references. None.

11.1.4.3. Literature search and risk assessment completed on. 05/06/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-*trans*-6-*cis*-dodecadienal would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-*trans*-6-*cis*-dodecadienal in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-*trans*-6-*cis*-dodecadienal 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).

11.1.5.3. Additional references. None.

11.1.5.4. Literature search and risk assessment completed on. 04/29/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-*trans*-6-*cis*-dodecadienal 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-*trans*-6-*cis*-dodecadienal. Based on the Creme RIFM Model, the inhalation exposure is 0.000016 mg/day. This exposure is 87500 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.

11.1.6.2. Additional references. None.

11.1.6.3. Literature search and risk assessment completed on. 05/04/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-*trans*-6-*cis*-dodecadienal 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-*trans*-6-*cis*-dodecadienal 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 2-*trans*-6-*cis*-dodecadienal 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, 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 $\geq$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), 2-*trans*-6-*cis*-dodecadienal presents no risk to the aquatic compartment in the screening-level

assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 2-*trans*-6-*cis*-Dodecadienal has been pre-registered for REACH with no additional information available at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.33			1000000	0.00233	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	4.32	4.32
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.00233 μg/L. The revised PEC/PNECs for EU 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.

11.2.4. Literature search and risk assessment completed on

05/05/21.

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**
- **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 05/14/21.

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.2021.112691.

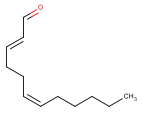
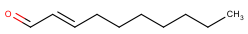
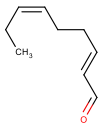
Appendix

Read-across Justification

Methods

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

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

	Target Material	Read-across Material	Read-across Material
Principal Name	2-*trans*-6-*cis*-Dodecadienal	2-Decenal (*trans*-2-Decenal)	Nona-2-*trans*-6-*cis*-dienal
CAS No.	21662-13-5	3913-71-1 (3913-81-3)	557-48-2
Structure			
Similarity (Tanimoto Score)		0.65	0.76
Read-across Endpoint		• Skin Sensitization	• Genotoxicity
Molecular Formula	$C_{12}H_{20}O$	$C_{10}H_{18}O$	$C_9H_{14}O$
Molecular Weight	180.29	154.25	138.21
Melting Point (°C, EPI Suite)	11.83	−8.92	−20.98
Boiling Point (°C, EPI Suite)	263.14	230.0	208.67
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.79	10.43	31.06
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.32	3.55	2.84
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	11.33	67.82	318.80
J_{max} (μg/cm^2/h, SAM)	1.675	28.634	58.691
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.82E+001	3.11E+001	2.06E+001
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• 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
DNA Binding (OECD QSAR Toolbox v4.2)	• Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition ≫ α,β- unsaturated aldehydes		• Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition ≫ α,β- unsaturated aldehydes
Carcinogenicity (ISS)	• α,β-unsaturated carbonyls (Genotox)|Structural alert for genotoxic carcinogenicity		• α,β-unsaturated carbonyls (Genotox)|Structural alert for genotoxic carcinogenicity
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found		• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• α,β-unsaturated carbonyls		• α,β-unsaturated carbonyls
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• α,β-unsaturated carbonyls		• α,β-unsaturated carbonyls
Oncologic Classification	• Aldehyde Type Compounds		• Aldehyde Type Compounds

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Skin Sensitization			
Protein Binding (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 | 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 ≫ Michael addition on α,β-Unsaturated carbonyl compounds|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 ≫ Polarized Alkenes|Michael addition ≫ Polarized Alkenes ≫ Polarized 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 ≫ Polarized Alkenes|Michael addition ≫ Polarized Alkenes ≫ Polarized alkene - aldehydes|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)	• Highly reactive (GSH)|Highly reactive (GSH) ≫ 2-Alken-1-als (MA)	
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	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• Alert for Michael acceptor	• Alert for Michael acceptor	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2 and 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on 2-*trans*-6-*cis*-dodecadienal (CAS # 21662-13-5). 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, nona-2-*trans*-6-*cis*-dienal (CAS # 557-48-2), 2-decenal (CAS # 3913-71-1), and *trans*-2-decenal (CAS # 3913-81-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 2-Decenal (CAS # 3913-71-1) and *trans*-2-decenal (CAS # 3913-81-3) were used as read-across analogs for the target material 2-*trans*-6-*cis*-dodecadienal (CAS # 21662-13-5) for the skin sensitization endpoint.
  - The target material and the read-across analogs are structurally similar and belong to a class of straight chain α,β-unsaturated aldehydes.
  - The target material and the read-across analog share an α,β-unsaturated aldehyde functionality.
  - The key difference between the target material and the read-across analog is the target material is a C12 straight chain aldehyde with 1 extra unsaturation in position 6, whereas the read-across analog is a C10 straight chain. This structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, 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 several skin sensitization-related alerts for Michael addition and Schiff base formation. Michael addition for α,β-unsaturated aldehydes involves the attack by a nucleophile at the β-carbon atom. A Schiff base formation mechanism has been suggested to be responsible for the protein binding ability of aldehydes. The data described in the skin sensitization section show that both target and read-across are skin sensitizers. Therefore, data are consistent with *in silico* alerts.
  - 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.

- Nona-2-*trans*-6-*cis*-dienal (CAS # 557-48-2) was used as read-across analogs for the target material 2-*trans*-6-*cis*-dodecadienal (CAS # 21662-13-5) for the genotoxicity endpoint.
  - The target material and the read-across analogs are structurally similar and belong to a class of straight chain α,β-unsaturated aldehydes.
  - The target material and the read-across analog share an α,β-unsaturated aldehyde functionality and a double bond in position 6.
  - The key difference between the target material and the read-across analog is the target material is a C12 straight chain aldehyde, whereas the read-across analog is a C9 straight chain aldehyde. This structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, 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 several skin sensitization-related alerts for Michael addition and Schiff base formation typical for α,β-unsaturated aldehydes. An initial Michael addition mechanism has been suggested to be primarily responsible for the ability of α,β-unsaturated aldehydes to alkylate DNA. A subsequent Schiff base reaction at the carbonyl can result in cross-linked DNA adducts. Additionally, compounds with an α,β-unsaturated carbonyl are bis-electrophile reactive molecules that may interact with electron-rich biological macromolecules. Because of conjugation with the carbonyl group, the β-carbon is positively polarized and becomes the preferred site of nucleophilic attack, as in a classic Michael type addition. In spite of a common structural feature, α,β-unsaturated carbonyl compounds can undergo different interactions with DNA, which lead to different genotoxic and mutagenic responses. The following genotoxic mechanisms are conceivable: formation of cyclic adducts, frameshift interaction, strand breaks, and crosslinking. In addition to direct interactions, other metabolic activations are conceivable, such as metabolic epoxidation and formation of radicals. The predominant interaction of α,β-unsaturated carbonyl compounds with DNA components is the formation of cyclic 1,N2-deoxyguanosine adducts. This reaction occurs through an initial Michael addition to the exocyclic nitrogen of deoxyguanosine (dG), followed by ring closure and formation of the 8-hydroxypropano adduct. Further reactions are also possible, including the formation of cross-links with proteins and nucleic acids. The data for the read-across analog confirm that the material does not pose a concern for genotoxicity. Therefore, the predictions are 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.

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