Food and Chemical Toxicology 161 (2022) 112917

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, 2-tridecenal, CAS registry number 7774-82-5

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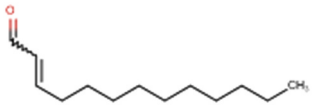
ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Conflicts of interest

The authors declare that they have no conflicts of interest.

Version: 111621. 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: 2-Tridecenal CAS Registry Number: 7774-82-5
Additional CAS Numbers*: 7069-41-2 *trans*-2-Tridecenal (No Reported Use)
*Included because the materials are isomers

Abbreviation/Definition List:

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https://doi.org/10.1016/j.fct.2022.112917
Received 18 November 2021; Accepted 8 March 2022
Available online 11 March 2022

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2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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., 2017; Safford et al., 2015a; Safford et al., 2017; Comiskey 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 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-Tridecenal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from analogs 2-dodecenal (CAS # 4826-62-4) and *trans*-2-dodecenal (CAS # 4826-62-4) show that 2-tridecenal is not expected to be genotoxic. Data on analog hexen-2-al (CAS # 6728-26-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from analog 2-decenal (CAS # 3913-71-1) provided 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 ultraviolet/visible (UV/Vis) spectra; 2-tridecenal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-tridecenal was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per International Fragrance Association (IFRA) Environmental Standards; 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, 2007a; RIFM, 2007b)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day (Gaunt et al., 1971)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 230 μg/cm^2 RIFM (2017)
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: 3.1 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 40.34 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 96-h Fish LC50: 0.147 mg/L (ECOSAR; US ECHA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Fish LC50: 0.147 mg/L (ECOSAR; US ECHA, 2012b)
RIFM PNEC is: 0.0147 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

Chemical Name: 2-Tridecenal	Chemical Name: trans-2-Tridecenal
CAS Registry Number: 7774-82-5	**CAS Registry Number:** 7069-41-2
Synonyms: ﾄﾘﾃﾞｾﾝ-2-ｱｰﾙ; Tridec-2-enal; Tridecenal-2-trans; 2-Tridecen-1-al; 2-Tridecenal	**Synonyms:** (E)-Tridecen-2-al; Tridec-2-enal
Molecular Formula: $C_{13}H_{24}O$	**Molecular Formula:** $C_{13}H_{24}O$
Molecular Weight: 196.33	**Molecular Weight:** 196.33
RIFM Number: 1069	**RIFM Number:** 5357

2. Physical data*

1. **Boiling Point:** 105 °C at 1 mm Hg (Fragrance Materials Association [FMA]), 274.55 °C (EPI Suite)
2. **Flash Point:** 210 °F (RIFM), 230 °F; CC (FMA)
3. **Log K_{OW}:** 5.3/5.7 (RIFM, 2013b), 5.02 (EPI Suite)
4. **Melting Point**: 23.34 °C (EPI Suite)
5. **Water Solubility:** 2.353 mg/L (EPI Suite)
6. **Specific Gravity:** 0.85 (FMA)
7. **Vapor Pressure:** 0.00439 mm Hg at 20 °C (EPI Suite v4.0), 0.4 mm Hg 20 °C (FMA), 0.00719 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})

9. **Appearance/Organoleptic:** Colorless oily liquid. Powerful, waxy-citrusy, peel-like odor of moderate tenacity. More citrusy than the odor of Tridecanal (Arctander, 1969).

*Physical data for both materials in this assessment are identical.

3. Volume of use (Worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00034% (RIFM, 2020a)
2. **Inhalation Exposure*:** 0.000017 mg/kg/day or 0.00013 mg/day (RIFM, 2020a)
3. **Total Systemic Exposure**:** 0.000032 mg/kg/day (RIFM, 2020a)

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

***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 Fragrance, inhalation exposure, and total exposure.

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 v3.1	OECD QSAR Toolbox v4.2
I	I	I

6.2. *Analogs Selected*

a. **Genotoxicity:** 2-Dodecenal (CAS # 4826-62-4); *trans*-2-dodecenal (CAS # 20407-84-5)
b. **Repeated Dose Toxicity:** Hexen-2-al (CAS # 6728-26-3)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 2-Decenal (CAS # 3913-71-1)
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

2-Tridecenal is reported to occur in the following foods by the VCF*:
Apple brandy (*calvados*)
Beef.
Coriander leaf (*Coriandrum sativum* L.)
Grape brandy.
Lamb and mutton
trans-2-Tridecenal is not reported to occur in foods by the VCF*.
*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Both materials pre-registered for 2010; no dossier available for either as of 11/16/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-tridecenal 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	0.0083
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)	0.0083
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)	0.0083
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-tridecenal, the basis was the reference dose of 2 mg/kg/day, a predicted skin absorption value of 40%, and 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).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-tridecenal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-Tridecenal was tested in the BlueScreen assay and was found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity in the presence and absence of metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive 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 activity of 2-tridecenal. Read-across material *trans*-2-dodecenal (CAS # 4826-62-4; see Section VI) was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using both the standard plate incorporation and modified preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 2-dodecenal in dimethyl sulfoxide (DMSO) at concentrations up to 1000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2007a). Based on the criteria of the assay, 2-dodecenal is considered non-mutagenic in the Ames assay, and this can be extended to 2-tridecenal.

There are no studies assessing the clastogenicity of 2-tridecenal. The clastogenicity of read-across material *trans*-2-dodecenal (CAS # 20407-84-5; see Section VI) was assessed in an *in vivo* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 474. Groups of male and female NMRI mice were treated with *trans*-2-dodecenal in corn oil via a single oral dose at concentrations of 500, 1000, and 2000 mg/kg body weight. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The frequencies of micronucleated erythrocytes were not increased in peripheral blood in the animals at the doses tested (RIFM, 2007b). Under the conditions of the study, 2-dodecenal was considered not clastogenic in the *in vivo* micronucleus test, and this can be extended to 2-tridecenal.

Based on the available data, 2-dodecenal and *trans*-2-dodecenal do not present a concern for genotoxic potential, and this can be extended to 2-tridecenal.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/12/21.

11.1.2. Repeated dose toxicity

The MOE for 2-tridecenal is sufficient for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 2-tridecenal. Read-across material hexen-2-al (CAS # 6728-26-3; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In a non-GLP and non-guideline subchronic study, 15 CFE rats/sex/dose were fed diets containing 0, 260, 640, 1600, or 4000 ppm hexen-2-al for 13 weeks (equivalent to 0, 13, 32, 80, or 200 mg/kg/day, respectively). No treatment-related mortality was reported for any dose group. No treatment-related changes in food consumption, bodyweight parameter, hematology, clinical chemistry, organ weights, and histopathology were reported. There was a slight increase in male urine volume with a concurrent decrease in the specific gravity of urine at the highest dose, but there were no alterations in kidney weight or histopathology. In the high-dose group females, ovary weight was significantly increased but without any correlating histopathological changes. Hence, these effects were not considered to be treatment-related adverse effects. Based on the lack of any treatment-related adverse effects at the highest tested dose, the NOAEL for repeated dose toxicity was considered to be 4000 ppm or 200 mg/kg/day.

Therefore, the 2-tridecenal MOE can be calculated by dividing the hexen-2-al NOAEL in mg/kg/day by the total systemic exposure to 2-tridecenal, 200/0.000032, or 6250000.

In addition, the total systemic exposure to 2-tridecenal (0.032 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Derivation of reference dose (RfD)

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, 2020c) and a reference dose of 2 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for 2-tridecenal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 200 mg/kg/day by the uncertainty factor, 100 = 2 mg/kg/day. See Table 1 for additional studies.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/16/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2-tridecenal or any read-across materials. The total systemic exposure to 2-tridecenal 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-tridecenal or any read-across materials evaluated that can be used to support the reproductive toxicity endpoints. The total systemic exposure to 2-tridecenal (0.032 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/03/21.

11.1.4. Skin sensitization

Based on the existing data and read-across 2-decenal (CAS # 3913-71-1), 2-tridecenal is considered a skin sensitizer with a defined NESIL of 230 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization data exist on 2-tridecenal. Based on existing data and read-across to 2-decenal (CAS # 3913-71-1; see Section VI), 2-tridecenal is considered a skin sensitizer. 2-Tridecenal and read-across material 2-decenal are predicted to be

Table 1
Available additional studies within inadequate study design for the treatment material.

Duration	Animals/Sex/Dose	GLP/Guidelines	Route	Doses	Adverse effects	NOAEL	Ref
28 days	5 male F344rats/dose	OECD 407	Oral gavage	0, 10, 30, 100 mg/kg/day	None	100	ECHA, 2017

Table 2
Data summary for 2-decenal as read-across for 2-tridecenal.

LLNA Weighted Mean EC3 Value [No. Studies] μg/cm^2	Potency Classification[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
625 [1]	Moderate	236	2760	NA	230

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

directly reactive to skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across material 2-decenal was found to be positive in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens™, and U-SENS™ tests (Natsch et al., 2013). In the local lymph node assay (LLNA), 2-tridecenal was found to be sensitizing with an EC3 value of 3.8% (950 μg/cm^2) (RIFM, 2012). In an LLNA with read-across material 2-decenal, the EC3 value was reported as 2.5% (625 μg/cm^2) (Roberts et al., 2007; Gerberick et al., 2005). In human maximization tests conducted on 26 and 29 subjects, no reactions indicative of sensitization were observed with 4% 2-tridecenal (2760 μg/cm^2) (RIFM, 1979). Similarly, in human maximization tests with read-across material 2-decenal at 4% or 2760 μg/cm^2 in petrolatum, no reactions indicative of sensitization were observed when used for induction and challenge (RIFM, 1973a; RIFM, 1977). In a Confirmation of No Induction in Humans (CNIH) test, no reactions indicative of sensitization were observed when read-across material 2-decenal at 0.125% in alcohol SDA 39C (97 μg/cm^2) and 2% in dimethyl phthalate (unknown patch size) was used for induction and challenge (RIFM, 1973b; RIFM, 1970). In a CNIH conducted according to Politano and Api (Politano and Api, 2008) with 0.2% w/v or 236 μg/cm^2 read-across trans-2-decenal in 1:3 Ethanol:DEP, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2017).

Based on the available data and read-across 2-decenal, 2-tridecenal is considered a skin sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 230 μg/cm^2 (see Table 2). 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, 2020c) and a reference dose of 2 mg/kg/day.

Additional References: Natsch et al., 2007; Natsch and Gfeller, 2008; McKim et al., 2010.

Literature Search and Risk Assessment Completed On: 06/26/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorbance spectra, 2-tridecenal 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-tridecenal in experimental models. UV/Vis absorption spectra indicate no 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, 2-tridecenal 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 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: 03/02/21.

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-tridecenal 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-tridecenal. Based on the Creme RIFM Model, the inhalation exposure is 0.00013 mg/day. This exposure is 10769 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-tridecenal 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, 2-tridecenal was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 2-tridecenal 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 $\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-tridecenal presents a 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-Tridecenal has been pre-registered for REACH with no additional data 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.

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

Exposure	Europe	North America
Log K_{ow} Used	5.7	5.7
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1*	<1*
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined regional volume of use for both CAS.

Based on available data, the RQs for these materials are <1. No further assessment is necessary.

The RIFM PNEC is 0.0147 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 03/11/21.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	0.16			1,000,000	0.00016	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.147	0.387	0.599	10,000	0.0147	Vinyl/Allyl Aldehydes
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.312	0.234	0.553			Neutral Organics SAR

- **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 11/16/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112917.

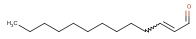
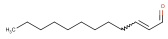
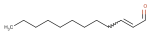
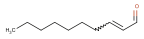
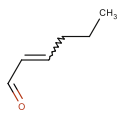
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020b). 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, 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, 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 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	Read-across Material	Read-across Material	Read-across Material
Principal Name	2-Tridecenal	2-Dodecenal	2-*trans*-Dodecenal	2-Decenal	Hexen-2-al
CAS No.	7774-82-5	4826-62-4	20407-84-5	3913-71-1	6728-26-3
Structure					
Similarity (Tanimoto Score)		0.98	0.98	0.86	0.64
Endpoint		Genotoxicity	Genotoxicity	Skin sensitization	Repeated dose toxicity
Molecular Formula	$C_{13}H_{24}O$	$C_{12}H_{22}O$	$C_{12}H_{22}O$	$C_{10}H_{18}O$	$C_6H_{10}O$
Molecular Weight	196.33	182.31	182.31	154.25	98.14
Melting Point (°C, EPI Suite)	23.34	12.85	12.85	−8.92	−55.63
Boiling Point (°C, EPI Suite)	274.55	257.92	257.92	230.00	146.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.96	2.37	2.37	10.43	629.28

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(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.35	7.26	7.26	67.82	5261.00
Log K_{OW}	5.02	4.53	4.53	3.55	1.58
J_{max} (μg/cm^2/h, SAM)	0.38	1.14	1.14	8.68	215.10
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	72.75	54.82	54.82	31.11	4.95
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	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 ≫ 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	Michael addition|Michael addition ≫ Polarised Alkenes-Michael addition|Michael addition ≫ Polarised 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	α, β-unsaturated carbonyls (Genotox)|Structural alert for genotoxic carcinogenicity		
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	α, β-unsaturated carbonyls		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	α, β-unsaturated carbonyls	α, β-unsaturated carbonyls	α, β-unsaturated carbonyls		
Oncologic Classification	Aldehyde-Type Compounds	Aldehyde-Type Compounds	Aldehyde-Type Compounds		
Repeated Dose Toxicity					
Repeated Dose (HESS)	Not categorized				Not categorized
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 ≫ 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	

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(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Protein Binding Potency	Highly reactive (GSH)|Highly reactive (GSH) ≫ 2-Alken-1-als (MA)			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 identified.			Alert for Michael Acceptor 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	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on the target material 2-tridecenal (CAS # 7774-82-5). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analogs 2-dodecenal (CAS # 4826-62-4), 2-trans-dodecenal (CAS # 20407-84-5), 2-decenal (CAS # 3913-71-1), and hexen-2-al (CAS # 6728-26-3) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusion

- 2-Dodecenal (CAS # 4826-62-4) was used as a read-across analog for the target material, 2-tridecenal (CAS # 7774-82-5), for the genotoxicity endpoint.
  - o The target substance and the read-across analog belong to the structural class of aliphatic aldehydes.
  - o The target substance and the read-across analog share an aldehyde functional group with α, β unsaturation.
  - o The key difference between the target substance and the read-across analog is that the target substance is a C13 molecule while the read analog is a C12 molecule. This structure difference between the target substance and the read-across analog is toxicologically insignificant.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the aldehyde functional group with the α, β unsaturated fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for toxicity endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog have carcinogenicity alert (low reliability) according to the ISS model. Both substances also have *in vitro* and *in vivo* mutagenicity alerts and are classified as aldehyde-type compounds. This shows that the read-across analog is predicted to have comparable reactivity with the target substance. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genetic toxicity.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural differences between the target material and the read-across analog do not affect consideration of the toxicity endpoints.
- 2-*trans*-Dodecenal (CAS # 20407-84-5) was used as a read-across analog for the target material, 2-tridecenal (CAS # 7774-82-5), for the genotoxicity endpoint.
  - o The target substance and the read-across analog belong to the structural class of aliphatic aldehydes.
  - o The target substance and the read-across analog share an aldehyde functional group with α, β unsaturation.
  - o The key difference between the target substance and the read-across analog is that the target substance is a C13 molecule while the read analog is a C12 molecule. This structure difference between the target substance and the read-across analog is toxicologically insignificant.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the aldehyde functional group with the α, β unsaturated fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 80\%$ for the target substance and $\leq 40\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} values indicates exposure to the substance, it does not represent

hazard or toxicity parameters. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for toxicity endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog both have carcinogenicity alerts (low predictability) according to the ISS model. Both substances also have *in vitro* and *in vivo* mutagenicity alerts and are classified as aldehyde-type compounds. This shows that the read-across analog is predicted to have comparable reactivity with the target substance. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genetic toxicity.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural differences between the target material and the read-across analog are toxicologically insignificant.
- 2-Decenal (CAS # 3913-71-1) was used as a read-across analog for the target material, 2-tridecenal (CAS # 7774-82-5), for the skin sensitization endpoint.
  - o The target substance and the read-across analog belong to the structural class of aliphatic aldehydes.
  - o The target substance and the read-across analog share an aldehyde functional group with α, β unsaturation.
  - o The key difference between the target substance and the read-across analog is that the target substance is a C13 molecule while the read analog is a C10 molecule. This structure difference between the target substance and the read-across analog is not toxicologically significant.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the aldehyde functional group with the α, β unsaturated fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties: $J_{max} \leq 40\%$ for the target substance and $\leq 80\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} values indicates exposure to the substance, it does not represent hazard or toxicity parameters. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for toxicity endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog have Michael acceptor alert by the skin sensitization reactivity domains in ToxTree. The target and the read-across analog also have several protein-binding alerts. This shows that the read-across analog is predicted to have comparable reactivity with the target substance. The data described in the skin sensitization section show that the read-across analog is considered to be a strong sensitizer, consistent with *in silico* alerts.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural differences between the target material and the read-across analog are toxicologically insignificant.
- Hexen-2-al (CAS # 6728-26-3) was used as a read-across analog for the target material, 2-tridecenal (CAS # 7774-82-5), for the repeated dose toxicity endpoint.
  - o The target substance and the read-across analog belong to the structural class of aliphatic aldehydes.
  - o The target substance and the read-across analog share an aldehyde moiety with α, β unsaturation.
  - o The key difference between the target substance and the read-across analog is that the target substance is a C13 molecule while the read-across analog is a C6 molecule. This structural difference between the target substance and the read-across analog is not toxicologically significant.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score are not toxicologically significant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for toxicological endpoints are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog are toxicologically insignificant.

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