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RIFM fragrance ingredient safety assessment, undecenal, CAS Registry Number 1337-83-3

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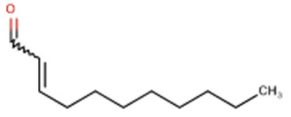
Name: Undecenal
CAS Registry Number: 1337-83-3
Additional CAS Numbers*:
53448-07-0 *trans*-2-Undecenal
2463-77-6 2-Undecenal



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*These additional materials are included in this assessment because they are a mixture of isomers.

Abbreviation/Definition List:

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

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(*continued*)

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

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

This safety assessment is based on the RIFM Criteria Document (Api, 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.

Undecenal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that undecenal is not genotoxic. Data on read-across 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, and the exposure to undecenal is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from read-across analog 2-decenal (CAS # 3913-71-1 provided undecenal 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; undecenal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; undecenal was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2003; RIFM, 2015b)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	Gaunt (1971)
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/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: Critical Measured Value: 83% (OECD 302C)	RIFM (1997)
Bioaccumulation:	
Screening-level: 9.071 L/kg	(EPI Suite 4.11; US EPA, 2012)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 0.0436 mg/L	RIFM (2017d)
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: 48-h *Daphnia magna* EC50: 0.0436 mg/L	RIFM (2017d)
RIFM PNEC is: 0.0436 μg/L	

- **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe <1

1. Identification

Chemical Name: Undecenal	Chemical Name: 2-Undecenal	Chemical Name: *trans*-2-Undecenal
CAS Registry Number: 1337-83-3	**CAS Registry Number:** 2463-77-6	**CAS Registry Number:**53448-07-0
Synonyms: Aldehyde Iso C11; ｳﾝﾃﾞｾﾅｰﾙ; Undec-2-enal; Intrelevenaldehyd spez.; Intreleven aldehyd spec.; Reaction mass of undec-8-enal and undec-9-enal and undec-10-enal; Intreleven aldehyde; Undecenoic aldehyde; Adenal C11; Undecenal	**Synonyms:** 2-Undecen-1-al; Undec-2-enal; Undecenal-2-*trans*; ｳﾝﾃﾞｾﾅｰﾙ	**Synonyms:** (E)-Undec-2-enal; 2-Undecenal, (E)-; Undec-2-enal
Molecular Formula: $C_{11}H_{20}O$	**Molecular Formula:** $C_{11}H_{20}O$	**Molecular Formula:** $C_{11}H_{20}O$
Molecular Weight: 168.8	**Molecular Weight:** 168.28	**Molecular Weight:** 168.8
RIFM Number: 5244	**RIFM Number:** 5007	**RIFM Number:** 5730

2. Physical data*

1. **Boiling Point:** 240.39 °C (EPI Suite), 77 °C at 0.27 kPa but at 101.5 kPa not distilled below 200 °C (473 K) with visible signs of decomposition at 200 °C (RIFM, 2013b)
2. **Flash Point:** 104 °C (Globally Harmonized System), 88.5 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2017c)
3. **Log K_{OW}:** 4.6 at 30 °C (RIFM, 1996b), 4.04 (EPI Suite), 4.7 (RIFM, 2013c)

4. **Melting Point**: 2.1 °C (EPI Suite), −33 °C (240 K) at 102.3 kPa (RIFM, 2013a)
5. **Water Solubility:** 22.27 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0291 mm Hg at 20 °C (EPI Suite v4.0), 0.0454 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:** Arctander, Volume II, 1969: Colorless liquid. Very powerful and diffusive, refreshingly citrusy-waxy, in dilution dry-floral, "clean" odor.

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

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.023% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.00016 mg/kg/day or 0.011 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.00050 mg/kg/day (RIFM, 2020b)

*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 Hydroalcoholics, inhalation exposure, and total exposure.

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   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:** 2-Dodecenal (CAS # 20407-84-5)
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

Undecenal is reported to occur in the following 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

Available for undecenal (ECHA, 2016); accessed 11/11/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for undecenal 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 undecenal, the basis was the reference dose of 2.0 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; December 2019).
[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, undecenal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Undecenal was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity without metabolic activation and negative for both cytotoxicity and genotoxicity with metabolic activation (RIFM, 2015c). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. While the BlueScreen assay on the target material showed positive results, data from additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenicity of undecenal was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using both the preincubation and the standard plate incorporation methods. *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1537 were treated with undecenal in dimethyl sulfoxide (DMSO) at concentrations up to 1000 μg/plate with and without metabolic activation. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2003). Under the conditions of the study, undecenal was not mutagenic in the Ames test.

The clastogenic activity of undecenal was assessed in an *in vitro* micronucleus assay conducted in accordance with GLP regulations and in compliance with OECD TG 487. Human peripheral blood lymphocytes were treated with undecenal in DMSO at concentrations ranging between 20 and 150 μg/mL in the presence and absence of metabolic activation. The percentage of cells with micronucleated binucleated cells in the test-substance-treated groups was not statistically significantly increased relative to vehicle control at any dose level (RIFM, 2015b). Based on the findings of this study, undecenal was concluded to be negative for the induction of micronuclei in both non-activated and S9-activated test systems in the *in vitro* mammalian cell micronucleus test using human peripheral blood lymphocytes.

Based on the data available, undecenal does not present a concern for genotoxic potential.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for undecenal 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 undecenal. Read-across material hexen-2-al (CAS # 6728-26-3; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In an OECD 407-compliant study, 5 male F344rats/dose were administered hexen-2-al via gavage for 28 days; the study was considered insufficient due to the limited sampling of only one sex (see Table 1). 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 (purity: 95%; boiling point: 149 °C) 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, body weight 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 (Gaunt, 1971).

Additional study data are presented in Table 1 below. However, these data are not sufficient to derive a NOAEL.

Therefore, the undecenal MOE can be calculated by dividing the hexen-2-al NOAEL in mg/kg/day by the total systemic exposure to undecenal, 200/0.00050, or 400000.

In addition, the total systemic exposure to undecenal (0.50 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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 (RfD) of 2 mg/kg/day.

11.1.2.1.1. Derivation of RfD. The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for undecenal 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.

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 undecenal or any read-across materials. The total systemic exposure to undecenal 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 undecenal or any read-across materials that can be used to support the reproductive toxicity endpoints. The total systemic exposure to undecenal (0.50 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 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 to 2-decenal (CAS # 3913-71-1), undecenal is considered a skin sensitizer with a defined NESIL of 230 μg/cm^2.

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

Table 1
Additional study data within inadequate study design for the treatment material.

Duration	Animals/Sex/Dose	GLP/Guidelines	Route	Doses	Adverse effects	NOAEL	Ref
28 days	5 male F344 rats/dose	OECD 407	Oral gavage	0, 10, 30, 100 mg/kg/day	None	100	ECHA (2018)

directly reactive to skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across 2-decenal was found to be positive in the *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens test, and U-SENS test (Natsch, 2013). Both materials have been tested in the murine local lymph node assay (LLNA) and found to be sensitizing. Undecenal was found to have an EC3 of 25% or 6250 μg/cm^2 (RIFM, 2012), and read-across analog 2-decenal was reported to have an EC3 of 2.5% or 625 μg/cm^2 (Roberts, 2007; Gerberick, 2005). Additionally, in an open epicutaneous test, undecenal did not induce reactions indicative of sensitization (RIFM, 1972). No reactions indicative of sensitization were observed with 2% undecenal in a Confirmation of No Induction in Humans test (CNIH) with 53 subjects (RIFM, 1973b). Similarly, in human maximization tests, no reactions were observed when read-across 2-decenal, at 4% or 2760 μg/cm^2 in petrolatum, was used for induction and challenge (RIFM, 1973a; RIFM, 1977). In a CNIH, no reactions indicative of sensitization were observed when read-across 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, 1973c; RIFM, 1970). In another CNIH conducted according to the method of Politano and Api (Politano, 2008) with 0.2% w/v or 236 μg/cm^2 read-across *trans*-2-decenal in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2017b).

Based on the weight of evidence (WoE) from the available data and read-across to 2-decenal, undecenal is considered a skin sensitizer with a 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 (2007); Natsch (2008); McKim (2010).

Literature Search and Risk Assessment Completed On: 02/26/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorbance spectra, undecenal 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 undecenal 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, 2009). Based on the lack of absorbance, undecenal 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/02/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for undecenal 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 undecenal. Based on the Creme RIFM Model, the inhalation exposure is 0.011 mg/day. This exposure is 127.3 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 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 undecenal 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, undecenal 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 undecenal 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

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

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 CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), undecenal presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. For CAS # 1337-83-3.

RIFM, 1996a: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test according to the OECD 301B method. Biodegradation of 69.7% was observed after 28 days.

RIFM, 1997: The Inherent biodegradability of the test material was determined by the respirometric method following the OECD 302C method. Mineral medium inoculated with fresh activated sludge and 30 mg/L of undecenal were stirred in closed flasks and incubated for up to 32 days. The biodegradation rate was greater than 70% by day 10 and was 83% after 28 days.

RIFM, 1996c: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Mineral medium inoculated with fresh activated sludge and 100 mg/L of undecenal were stirred in a closed flask for up to 28 days. The biodegradation rate was 49% at the end of the 10-day window and was 53% after 28 days.

RIFM, 2017e: The ready biodegradability of the test material was evaluated using the headspace test according to the OECD 310 guideline. Biodegradation of 48% was observed after 28 days.

RIFM, 2015d: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 74% was observed after 62 days.

11.2.2.1.2. Ecotoxicity. For CAS # 1337-83-3.

RIFM, 2017d: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under semi-static conditions in a closed system with no headspace. The 48-h EC50 value based on mean measured concentration was reported to be 0.0436 mg/L.

RIFM, 2017a: The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions in a closed system. The 72-h EC50 values based on time-weighted average concentration for growth rate and yield were reported to be 0.178 mg/L and 0.0575 mg/L, respectively.

11.2.2.1.3. Other available data. Undecenal has been registered under REACH with the following additional data available at this time (ECHA, 2016):

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value based on measured concentration for growth rate was reported to be 47.3 mg/L.

The following studies are available for read-across material 2-dodecenal (CAS # 20407-84-5; see Section VI):

RIFM, 2013d: The ready biodegradability of the test material was evaluated using the OECD 301F guideline. Biodegradation of 80% was observed after 28 days.

RIFM, 2014: A fish (*Oryzias latipes*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 value based on the arithmetic mean measured concentration was reported to be 0.718 mg/L (95% CI: 0.6473–0.7964 mg/L).

RIFM, 2016a: *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The study was conducted with a saturated solution with a nominal loading of 10 mg/L of the test material and further 4 dilution levels in a geometric series with a separation factor of 2.2 (nominal loading rates of 4.27%–45.5%). The 48-h EL50 based on nominal loading levels was reported to be 4.76 mg/L.

RIFM, 2016b: The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. Five loading levels of the test material in a geometric series with a separation factor of 3.16, prepared by diluting the saturated solution with dilution water, were tested as follows: 0.316–1.00 – 3.16–10.0 – 31.6–100% of the saturated solution. The 72-h EL50 values based on nominal loading levels for growth rate and yield were reported to be >100% of the test item.

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, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.7	4.7
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100*	1–10*
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined regional volume of use.

Based on read-across, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.0436 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: 03/12/21.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.019			1000000	0.001019	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.156	2.099	2.297	10000	0.0156	Vinyl/Allyl aldehydes
ECOSAR Acute Endpoints **(Tier 2)** v1.11	2.039	1.398	2.267			Neutral Organics SAR
Tier 3: Measured Data (including read-across data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.718					
Daphnia		0.0436		1000	0.0436	
Algae		0.0575				

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 11/11/21.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113052.

Appendix

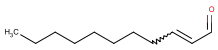
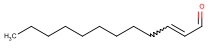
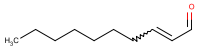
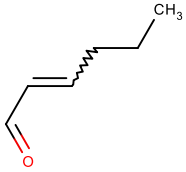
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). 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
Principal Name	Undecenal	2-Dodecenal	2-Decenal	Hexen-2-al
CAS No.	1337-83-3	20407-84-5	3913-71-1	6728-26-3
Structure				
Similarity (Tanimoto Score)		0.84	0.98	0.64
Endpoint		Environmental	Skin Sensitization	Repeated dose toxicity
Molecular Formula	$C_{11}H_{20}O$	$C_{12}H_{22}O$	$C_{10}H_{18}O$	$C_6H_{10}O$
Molecular Weight	168.28	182.31	154.25	98.14
Melting Point (°C, EPI Suite)	2.10	12.85	−8.92	−55.63
Boiling Point (°C, EPI Suite)	240.39	257.92	230.00	146.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	6.05	2.37	10.43	629.28
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	22.27	7.26	67.82	5261.00
Log K_{OW}	4.04	4.53	3.55	1.58
J_{max} (μg/cm^2/h, SAM)	3.24	1.14	8.68	215.10
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	41.24	54.82	31.11	4.95
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	
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	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)				

Summary

There are insufficient toxicity data on the target material, undecenal (CAS # 1337-83-3). 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, 2-decenal (CAS # 3913-71-1), 2-dodecenal (CAS # 20407-84-50), and hexen-2-al (CAS # 6728-26-3) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusion

- 2-Decenal (CAS # 3913-71-1) was used as a read-across analog for the target material undecenal (CAS # 1337-83-3) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to the structural class of aliphatic aldehydes.
  - o The target material and the read-across analog share an α,β-unsaturated aldehyde moiety.
  - o The key difference between the target material and the read-across analog is that the target material is a C11 molecule, while the read-across analog is a C10 molecule. This structure difference is toxicologically insignificant.
  - o The similarity between the target material 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 toxicologically insignificant.
  - o The physical–chemical properties of the target material 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 material and the read-across analog.
  - o The target material and the read-across analog have Michael acceptor alert for skin sensitization reactivity domains in Toxtree. The target material and the read-across analog also have several protein-binding alerts. Thus, the target material and the read-across analog are predicted to have comparable reactivity. The data described in the skin sensitization section shows that the read-across analog is considered to be a sensitizer, consistent with *in silico* alerts.
  - o The target material 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-Dodecenal (CAS # 20407-84-50) was used as a read-across analog for the target material undecenal (CAS # 1337-83-3) for the environmental endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of α,β-unsaturated straight-chain aldehydes.
  - o The target material and the read-across analog share an α,β-unsaturated aldehyde moiety.
  - o The key difference between the target material and the read-across analog is that the target material is a C11 molecule while the read-across analog is a C12 molecule. This structural difference is not significant.
  - o The similarity between the target material 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 insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their properties.
  - o The target material 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 not significant for this evaluation.
- Hexen-2-al (CAS # 6728-26-3) was used as a read-across analog for the target material undecenal (CAS # 1337-83-3) for the repeated dose toxicity.
  - o The target material and the read-across analog belong to the structural class of aliphatic aldehydes.
  - o The target material and the read-across analog share an aldehyde moiety with α,β-unsaturation.
  - o The key difference between the target material and the read-across analog is that the target material is a C11 molecule while the read-across analog is a C6 molecule. This structural difference between the target material and the read-across analog is not toxicologically significant.
  - o The similarity between the target material 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 material 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 material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for 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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