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RIFM fragrance ingredient safety assessment, 11-tridecen-6-one, 8,12-dimethyl-, CAS Registry Number 68141-18-4

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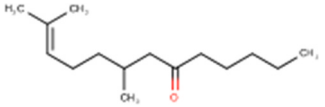

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Name: 11-Tridecen-6-one, 8,12-dimethyl-
CAS Registry Number: 68,141-18-4

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

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CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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.

11-Tridecen-6-one, 8,12-dimethyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 6,10-dimethylundeca-5,9-dien-2-one (CAS # 689-67-8) show that 11-tridecen-6-one, 8,12-dimethyl- is not expected to be genotoxic. Data on analog 6-methylhept-5-en-2-one (CAS # 110-93-0) 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 II material; exposure is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). Data from analog tetrahydro-pseudo-ionone (CAS # 1322-58-3) provided 11-tridecen-6-one, 8,12-dimethyl- a No Expected Sensitization Induction Level (NESIL) of 9400 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 11-tridecen-6-one, 8,12-dimethyl- is not expected to be phototoxic/photoallergenic. 11-Tridecen-6-one, 8,12-dimethyl- was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2003; RIFM, 2017a)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day. RIFM (2002b)
Reproductive Toxicity: No NOAEL Available. Exposure is below the TTC.
Skin Sensitization: NESIL = 9400 μg/cm^2. RIFM (1988)
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: 2.97 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 1766 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 0.314 mg/L (RIFM Framework; Salvito, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 0.314 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.000314 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 11-Tridecen-6-one, 8,12-dimethyl-
2. **CAS Registry Number: 68,141–18–4**
3. **Synonyms:** 8,12-Dimethyltridec-11-en-6-one; 8,12-Dimethyl-11-tridecen-6-one; 11-Tridecen-6-one, 8,12-dimethyl-
4. **Molecular Formula:** $C_{15}H_{28}O$
5. **Molecular Weight:** 224.38
6. **RIFM Number:** 6390
7. **Stereochemistry:** Stereoisomer not specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 283.19 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 5.43 (EPI Suite)
4. **Melting Point**: 26.62 °C (EPI Suite)
5. **Water Solubility:** 0.7581 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0046 mm Hg at 20 °C (EPI Suite v4.0), 0.00807 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

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

4. Exposure to fragrance ingredient

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00046% (RIFM, 2017b)
2. **Inhalation Exposure*:** 0.0000042 mg/kg/day or 0.00033 mg/day (RIFM, 2017b)
3. **Total Systemic Exposure**:** 0.000016 mg/kg/day (RIFM, 2017b)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class II, Intermediate* (Expert Judgment)

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

*See the Appendix below for further details.

6.2. Analogs Selected

a. **Genotoxicity:** 6,10-Dimethylundeca-5,9-dien-2-one (CAS # 689-67-8)
b. **Repeated Dose Toxicity:** 6-Methylhept-5-en-2-one (CAS # 110-93-0)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Tetrahydro-pseudo-ionone (CAS # 1322-58-3)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across Justification

See Appendix below

7. Metabolism

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

8. Natural occurrence

11-Tridecen-6-one, 8,12-dimethyl- 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

Pre-registered for 2010; no dossier available as of 04/15/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 11-tridecen-6-one, 8,12-dimethyl- are detailed below (Table 1).

Table 1
Maximum acceptable concentrations in finished products for 11-tridecen-6-one, 8,12-dimethyl-.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.00024
2	Products applied to the axillae	0.22
3	Products applied to the face/body using fingertips	0.20
4	Products related to fine fragrances	4.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.38
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.20
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.037
5D	Baby cream, oil, talc	0.012
6	Products with oral and lip exposure	0.00024
7	Products applied to the hair with some hand contact	0.048
8	Products with significant ano-genital exposure (tampon)	0.012
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.85
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.00024
10B	Aerosol air freshener	5.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.012
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 11-tridecen-6-one, 8,12-dimethyl-, the basis was the reference dose of 0.50 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 9400 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 v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 11-tridecen-6-one, 8,12-dimethyl- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 11-Tridecen-6-one, 8,12-dimethyl was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2014). 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 mutagenicity of 11-tridecen-6-one, 8, 12-dimethyl-. The mutagenic activity of read-across material 6,10-dimethylundeca-5,9-dien-2-one (CAS # 689-67-8; see Section VI) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 6,10-dimethylundeca-5,9-dien-2-one in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2003). Under the conditions of the study, 6,10-dimethylundeca-5,9-dien-2-one was not mutagenic in the Ames test, and this can be extended to 11-tridecen-6-one, 8, 12-dimethyl-.

There are no studies assessing the clastogenicity of 11-tridecen-6-one, 8,12-dimethyl-. The clastogenic activity of 6,10-dimethylundeca-5,9-dien-2-one was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 6,10-dimethylundeca-5,9-dien-2-one in DMSO at concentrations up to 1943 μg/mL in the presence and absence of S9 for 3 h and in the absence of metabolic activation for 24 h 6,10-Dimethylundeca-5,9-dien-2-one did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2017a). Under the conditions of the study, 6,10-dimethylundeca-5,9-dien-2-one was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 11-tridecen-6-one, 8, 12-dimethyl-.

Based on the data available, 11-tridecen-6-one, 8,12-dimethyl does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.2. Repeated dose toxicity

The MOE for 11-tridecen-6-one, 8,12-dimethyl- is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data for 11-tridecen-6-one, 8,12-dimethyl-. Read-across material 6-methylhept-5-en-2-one (CAS # 110-93-0; see Section VI) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. An OECD 408/GLP oral gavage 90-day subchronic study was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered test material 6-methylhept-5-en-2-one (methylheptenon) via oral gavage at doses of 0, 50, 200, or 1000 mg/kg/day in olive oil for 13 weeks. At 1000 mg/kg/day, there was a statistically significant reduction in food consumption (up to 13%) in females from days 28–49. The body weight of high-dose males was decreased throughout the study period, with a maximum decrease of 7.2% on day 91. The bodyweight changes of these high-dose males also decreased continuously, though it did not reach statistical significance. Body weight in high-dose females was statistically significantly decreased (6.7%) on day 63 only, whereas the bodyweight change in females of this dose group was statistically significantly decreased (up to 16.4%) from days 35–84, with the exception of day 70. There was a statistically significant decrease in food efficiency among high-dose males on days 21, 35, 63, and 77. High-dose animals were reported to have increased platelet counts, calcium, total protein, albumin, cholesterol levels, and a decrease in aspartate aminotransferase levels. There were increases in alkaline phosphatase, cloudy urine specimens, urinary blood, renal tubular, epithelial cells, degenerated transitional epithelial cells, granular casts, and epithelial cell casts in high-dose males. Further, increased inorganic phosphate, urea, total bilirubin, globulins, and magnesium, and a decrease in chloride levels were observed in high-dose females. There was a dose-related statistically significant increase in the absolute and relative kidney weight in males of the high- (absolute: 28.0%; relative: 38.7%), mid- (absolute: 16.5%; relative: 16.3%), and low-dose groups (absolute: 14.3%; relative: 11.6%) and in females of the high-dose group (absolute: 14.3%; relative: 21.6%). There was a statistically significant increase in the absolute (males: 29.6%; females: 21.9%) and relative (males: 40.7%; females: 29.7%) liver weights among both sexes of the high-dose group. Centrilobular hypertrophy of liver cells was observed in all animals of the high-dose group. At 200 mg/kg/day, increased calcium, total protein, albumin, and cholesterol levels in males and increased platelet counts in females were observed. The increased kidney weights in all treated males corresponded to an increased accumulation of α-2u-globulin in the renal cortex of all-male rats (confirmed with Mallory-Heidenhain stain). These kidney changes were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman, 1992; Lehman-McKeeman, 1990). Under the conditions of the study, the NOAEL was considered to be 50 mg/kg/day, based on increased platelet counts among mid-dose females and high-dose animals, as well as decreased body weights among high-dose animals (RIFM, 2002b).

Therefore, the 11-tridecen-6-one, 8,12-dimethyl- MOE for the repeated dose toxicity endpoint can be calculated by dividing the 6-methylhept-5-en-2-one NOAEL in mg/kg/day by the total systemic exposure to 11-tridecen-6-one, 8,12-dimethyl-, 50/0.000016, or 3125000.

In addition, the total systemic exposure to 11-tridecen-6-one, 8,12-dimethyl- (0.016 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II 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, 2020b) and a reference dose of 0.50 mg/kg/day.

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 reference dose for 11-tridecen-6-one, 8,12-dimethyl- was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 50 mg/kg/day by the uncertainty factor, 100 = 0.50 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/04/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 11-tridecen-6-one, 8,12-dimethyl- or any read-across materials. The total systemic exposure to 11-tridecen-6-one, 8,12-dimethyl- is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2,4,4,7-tetramethyl-6-octen-3-one or any read-across materials that can be used to support the reproductive toxicity endpoints. The total systemic exposure (0.016 μg/kg/day) is below the TTC for 2,4,4,7-tetramethyl-6-octen-3-one (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/05/20.

11.1.4. Skin sensitization

Based on the existing data and read-across to tetrahydro-pseudo-ionone (CAS # 1322-58-3), 11-tridecen-6-one, 8,12-dimethyl- is considered a skin sensitizer with a defined NESIL of 9400 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 11-tridecen-6-one, 8,12-dimethyl-. Based on the existing data and read-across analog tetrahydro-pseudo-ionone (CAS # 1322-58-3; see Section VI), 11-tridecen-6-one, 8,12-dimethyl- is considered a skin sensitizer with a NESIL of 9400 μg/cm^2. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts, 2007; OECD Toolbox v4.2). Additionally, in a murine Local Lymph Node Assay (LLNA), 11-tridecen-6-one, 8, 12-dimethyl- was found to be sensitizing with an EC3 value of 34.1% (8525 μg/cm^2) (RIFM, 2002a). In a human maximization test, skin sensitization reactions were present in 2 studies and absent in 1 study with 8% (5520 μg/cm^2) read-across analog tetrahydro-pseudo-ionone in petrolatum (RIFM, 1982; RIFM, 1977; RIFM, 1978). However, in a Confirmation of No Induction in Humans test (CNIH) with 9448 μg/cm^2 of read-across analog tetrahydro-pseudo-ionone in 3:1 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 106 volunteers (RIFM, 1988).

Based on the weight of evidence (WoE) from structural analysis, an animal study, and read-across analog tetrahydro-pseudo-ionone, 11-tridecen-6-one, 8,12-dimethyl- is considered a weak sensitizer with a WoE NESIL of 9400 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, 2020b) and a reference dose of 0.50 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 11-tridecen-6-one, 8,12-dimethyl- would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 2
Data summary for read-across material tetrahydro-pseudo-ionone and 11-tridecen-6-one, 8,12-dimethyl-.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
8525 [1]	Weak	9488	N/A	5520	9400

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.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 11-tridecen-6-one, 8,12-dimethyl- in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 11-tridecen-6-one, 8, 12-dimethyl- does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 11-tridecen-6-one, 8,12-dimethyl- is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 11-tridecen-6-one, 8,12-dimethyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.00033 mg/day. This exposure is 1424 times lower than the Cramer Class III* TTC value of 0.47 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 11-tridecen-6-one, 8,12-dimethyl- 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 tables below (see Tables 3 and 4). 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, 11-tridecen-6-one, 8,12-dimethyl- 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 11-tridecen-6-one, 8,12-dimethyl- 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

Table 3
PNEC derivation.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.314	N/A	N/A	1,000,000	0.000314	N/A

Table 4
Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.43	5.43
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

and toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥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), 11-tridecen-6-one, 8,12-dimethyl- presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 11-Tridecen-6-one, 8,12-dimethyl 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 (Table 3).

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

The RIFM PNEC is 0.000314 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: 11/06/20.

12. Literature Search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/15/21.

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 G. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2021.112491.

Appendix

Read-across Justification

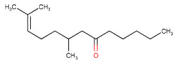
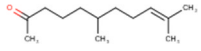
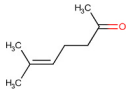
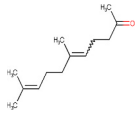
Methods

The read-across analogs (see Table 5) were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria

(RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

Table 5
Read-across analogs by endpoint

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	11-Tridecen-6-one, 8,12-dimethyl-	Tetrahydro-pseudo-ionone	6-Methyl-5-hepten-2-one	6,10-Dimethylundeca-5,9-dien-2-one
CAS No.	68,141-18-4	1322-58-3	110-93-0	689-67-8
Structure				
Similarity (Tanimoto Score)		0.7	0.4	0.7
Read-across Endpoint		• Skin Sensitization	• Repeated Dose	• Genotoxicity
Molecular Formula	$C_{15}H_{28}O$	$C_{13}H_{24}O$	$C_8H_{14}O$	$C_{13}H_{22}O$
Molecular Weight	224.39	196.34	126.20	194.32
Melting Point (°C, EPI Suite)	26.62	5.66	−40.02	6.85
Boiling Point (°C, EPI Suite)	283.19	250.01	164.35	260.99
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.08	5.88	238	3.35
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.43	4.44	2.06	4.36
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.75	7.32	1651	8.86
J_{max} (μg/cm^2/h, SAM)	0.935	4.821	109.105	7.816
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.56E+002	8.87E+001	2.15+E001	9.20E+001
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found			• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found			• No alert found
Carcinogenicity (ISS)	• No alert found			• No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found			• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found			• No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found			• No alert found
Oncologic Classification	• No alert found			• No alert found
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	
Skin Sensitization				
Protein Binding (OASIS v1.1)	• No alert found	• No alert found		
Protein Binding (OECD)	• No alert found	• No alert found		
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)		
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found		
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No skin sensitization reactivity domains alert identified.	• No skin sensitization reactivity domains alert 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

Summary

There are insufficient toxicity data on 11-tridecen-6-one, 8,12-dimethyl-, (CAS # 68,141-18-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, tetrahydro-pseudo-ionone (CAS # 1322-58-3), 6-methyl-5-hepten-2-one (CAS # 110-93-0), and 6,10-dimethylundeca-5,9-dien-2-one (CAS # 689-67-8) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Tetrahydro-pseudo-ionone (CAS # 1322-58-3) is used as a read-across analog for the target material 11-tridecen-6-one, 8,12-dimethyl- (CAS # 68,141-18-4) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of aliphatic unsaturated, branched ketones.
  - o The key difference between the target material and the read-across analog is the type of branching and length of the aliphatic chain on either side of the ketone group. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the ketone group. 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 OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Data for the read-across analogs are 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 alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 6-Methyl-5-hepten-2-one (CAS # 110-93-0) is used as a read-across analog for the target material 11-tridecen-6-one, 8,12-dimethyl- (CAS # 68,141-18-4) for the repeated dose toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of aliphatic unsaturated, branched ketones.
  - o The key difference between the target material and the read-across analog is the type of branching and length of the aliphatic chain on either side of the ketone group. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the ketone group. 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 OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Data for the read-across analogs are 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 alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 6,10-Dimethylundeca-5,9-dien-2-one (CAS # 689-67-8) is used as a read-across analog for the target material 11-tridecen-6-one, 8,12-dimethyl- (CAS # 68,141-18-4) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of aliphatic unsaturated, branched ketones.
  - o The key difference between the target material and the read-across analog is the type of branching and length of the aliphatic chain on either side of the ketone group. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the ketone group. 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 OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Data for the read-across analogs are 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 alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree.

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q17. Readily hydrolyzed to a common terpene? No.
Q19. Open chain? Yes.
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for a detailed explanation)? Yes.
Q21.3 or more different functional groups? No.
Q18. One of the list (see Cramer et al., 1978 for a detailed explanation on the list of categories)? Yes, Class II (Class Intermediate).

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