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Short Review

RIFM fragrance ingredient safety assessment, 2-undecanone, CAS Registry Number 112-12-9

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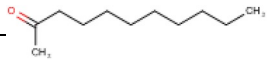

Name: 2-Undecanone
CAS Registry Number: 112-12-9

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

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AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
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-Undecanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-heptanone (CAS # 110-43-0) show that 2-undecanone is not genotoxic and that there are no safety concerns for 2-undecanone for skin sensitization under the current declared levels of use. The repeated dose and reproductive toxicity endpoints were completed using data from read-across analog 2-heptanone (CAS # 110-43-0), which provided an MOE > 100. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material, and the exposure to 2-undecanone is below the TTC (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on data and UV spectra. The environmental endpoints were evaluated; 2-undecanone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (EPA HPVIS; US EPA, 1998; ECHA Dossier: Heptan-2-one; ECHA, 2012a)
Repeated Dose Toxicity: NOAEL = 1087 mg/kg/day. (Lynch et al., 1981)
Reproductive Toxicity: Developmental Toxicity NOAEL = 500 mg/kg/day. Fertility NOAEL = 1239 mg/kg/day.
(US EPA Pilot Prenatal Developmental Study of 2-Heptanone; US EPA, 1993; ECHA Dossier: Heptan-2-one; ECHA, 2012a)
Skin Sensitization: No safety concerns under the current, declared levels of use.
(ECHA Dossier: Heptan-2-one; ECHA, 2012a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.
(UV Spectra, RIFM DB; RIFM, 1974c)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 85.4% (OECD 301B) (Creaven et al., 1964)
Bioaccumulation: Screening-level: 9.8 L/kg US EPA (2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 2.797 mg/L US EPA (2012a)
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: 48-h *Daphnia magna* LC50: 2.797 mg/L US EPA (2012a)
RIFM PNEC is: 0.2797 µg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: < 1

1. Identification

1. Chemical Name: 2-Undecanone
2. CAS Registry Number: 112-12-9
3. Synonyms: 2-Hendecanone; Methyl nonyl ketone; M.N.K.; Nonyl methyl ketone; 2-Oxoundecane; 'Rue ketone'; アルキル(C = 1 ~ 16) メチルケトン; Undecan-2-one; 2-Undecanone
4. Molecular Formula: $C_{11}H_{22}O$
5. Molecular Weight: 170.3
6. RIFM Number: 600
7. Stereochemistry: Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 231 °C (FMA Database), 224.03 °C (US EPA, 2012a)
2. **Flash Point:** 90 °C (GHS)
3. **Log K_{OW}:** 3.69 (US EPA, 2012a)
4. **Melting Point**: 10 °C (FMA Database), 3.83 °C (US EPA, 2012a)
5. **Water Solubility:** 19.71 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.833 (FMA Database)
7. **Vapor Pressure:** 0.0741 mm Hg @ 20 °C (US EPA, 2012a), 0.03 mm Hg 20 °C (FMA Database), 0.112 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless to pale yellow clear liquid with a waxy, fruity, ketonic with fatty pineapple nuances.*

*http://www.thegoodscentscompany.com/data/rw1021151.html, 09/15/17.

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA , 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0022% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000036 mg/kg/day or 0.0028 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00050 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

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

2. Analogs Selected:
   a. **Genotoxicity:** 2-Heptanone (CAS # 110-43-0)
   b. **Repeated Dose Toxicity:** 2-Heptanone (CAS # 110-43-0)
   c. **Reproductive Toxicity:** 2-Heptanone (CAS # 110-43-0)
   d. **Skin Sensitization:** 2-Heptanone (CAS # 110-43-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

7. Natural occurrence (discrete chemical) or composition (NCS)

2-Undecanone is reported to occur in the following by the VCF*:

Allium species	Lamb and mutton
Apple brandy (*Calvados*)	Lemon grass oil (*Cymbopogon*)
Asparagus (*Asparagus officinalis* L.)	Maize (*Zea mays* L.)
Banana (*Musa sapientum* L.)	Malt
Beef	Mastic (*Pistacia lentiscus*)
Beer	Mate (*Ilex paraguayensis*)
Black currants (*Ribes nigrum* L.)	Matsutake (*Tricholoma matsutake*)
Blue cheeses	Milk and milk products
Brazil nut (*Bertholletia excelsa*)	Miso (soy bean, rice or fish)
Buckwheat	Mushroom
Capsicum species	Olive (*Olea europaea*)
Cardamom (*Ellettaria cardamomum* Maton.)	Origanum (Spanish) (*Coridothymus cap.* (L.) Rchb.)
Caviar	Passion fruit (*Passiflora* species)
Cheddar cheese	Peach (*Prunus persica* L.)
Cheese, various types	Peanut (*Arachis hypogaea* L.)
Chicken	Peas (*Pisum sativum* L.)
Citrus fruits	Pepper (*Piper nigrum* L.)
Clam	Plum brandy
Cloves (*Eugenia caryophyllata* Thunberg)	Potato (*Solanum tuberosum* L.)
Coconut (*Cocos nucifera* L.)	Raspberry, blackberry and boysenberry
Coffee	Rice (*Oryza sativa* L.)
Crayfish	Rooibos tea (*Aspalathus linearis*)
Curcuma species	Rum
Date (*Phoenix dactylifera* L.)	Shrimps (prawn)
Elderberry (*Sambucus nigra* L.)	Starfruit (*Averrhoa carambola* L.)
Filbert, hazelnut (*Corylus avellano*)	Strawberry (*Fragaria* species)
Fish	Swiss cheeses
Ginger (*Zingiber* species)	Tea
Grape brandy	*Vaccinium* species
Guava and feyoa	Water yam (*Dioscorea alata*)

*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.

8. IFRA standard

None.

9. REACH dossier

Available; accessed 11/12/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.2. Risk assessment

2-Undecanone was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of 2-undecanone; however, read-across can be made to 2-heptanone (CAS # 110-43-0; see Section 5). The mutagenic activity of 2-heptanone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 2-heptanone in DMSO at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (US EPA, 1998). Under the conditions of the study, 2-heptanone was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 2-undecanone; however, read-across can be made to 2-heptanone (CAS # 110-43-0; see Section 5). The clastogenicity of 2-heptanone was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovary cells were treated with 2-heptanone in DMSO at concentrations up to 1200 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, either with or without S9 metabolic activation (https://echa.europa.eu/registration-dossier/-/registered-dossier/10230/7/7/2/?documentUUID=4ac9f4ea-74e8-4662-9feb-b72025d80c2a).%20 ECHA, 2012a). Under the conditions of the study, 2-heptanone was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, 2-heptanone does not present a concern for genotoxic potential and this can be extended to 2-undecanone.

Additional References: Kreja and Seidel, 2002; Kreja and Seidel, 2001; Albro et al., 1984; Nakajima et al., 2006.

Literature Search and Risk Assessment Completed On: 08/28/17.

10.1.3. Repeated dose toxicity

The margin of exposure for 2-undecanone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

There are no repeated dose toxicity data on 2-undecanone. Read-across material 2-heptanone (CAS # 110-43-0; see Section 5) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. In a 13-week oral gavage study conducted prior to GLPs, groups of 15 CFE rats/sex/dose were administered 2-heptanone via oral intubation at doses of 0, 20, 100, or 500 mg/kg/day in corn oil. An additional 5 rats/sex/dose receiving daily doses of 0, 100, or 500 mg/kg/day 2-heptanone were examined after 2 and 6 weeks. There were statistically significant increases in the number of cells excreted in the urine of both males and females at the mid- and high-dose groups after 13 weeks and in the high-dose group after 6 weeks, along with pale kidneys observed in the animals. A significant increase in the absolute liver weight (females) and relative kidney weights (males) was reported at the mid-dose. A significant increase in the absolute and relative liver weights (males and females, and males at week 6), absolute and relative kidney weights (males), and absolute stomach weights (females) were reported at the high-dose. Although organ weight changes were observed in the mid- and high-dose groups, no histopathological alterations or clinical chemistry changes were noted that might also be reflective of renal or hepatic toxicity. The NOAEL in this study was considered to be 20 mg/kg/day, based on the observed increase in urine cellularity and organ weight changes in the mid- and high-dose groups (Gaunt et al., 1972).

In a subchronic inhalation study conducted prior to GLPs, groups of 50 male Sprague Dawley rats and 8 male Cynomolgus monkeys (*Macaca fascicularis* strain) were exposed via inhalation to 0, 100, or 1000 ppm of 2-heptanone for 6 h/day, 5 days/week, for up to 10 months in whole-body chambers. Actual exposure levels were reported to be approximately 0, 131 ± 30 ppm or 1025 ± 136 ppm. No treatment-related effects in clinical signs, body weight, overall cardiopulmonary status, and gross or histopathological alterations were observed for both species. Thus, the NOAEC for both the rat and monkey was considered to be 1025 ppm, the highest dose tested based on the absence of any dose-dependent changes indicative of toxicity. Using standard minute volume and bodyweight values for male Sprague Dawley rats in a chronic study, the calculated NOAEL for repeated dose toxicity was considered to be 1087 mg/kg/day. For the monkeys, using standard minute volume and bodyweight values (BW of 4.5 kg, MV of 1.729 L/min), the calculated NOAEL was considered to be 662 mg/kg/day (Lynch et al., 1981).

In an OECD 421/GLP combined reproductive/developmental screening study, 2-heptanone was administered to groups of 12 Sprague Dawley rats/sex via inhalation at target concentrations of 0, 80, 400, or 1000 ppm (actual measured concentrations of 0, 79, 406, or 1023 ppm) for 6 h/day, 7 days/week during premating, mating, gestation day (GD) and early lactation for a total of 50 exposure days for males and 34–47 exposure days for females. A dose-related reduction in activity (less movement, decreased alertness and slower response to tapping on the chamber wall) was observed at 400 and 1000 ppm animals, that declined over the course of exposure as the animals appeared to acclimate to the vapor. The mean bodyweight change for the 400 ppm dam between GDs 0 and 7 was significantly lower than the controls. Males and females at 1000 ppm exhibited significantly decreased food consumption during days 0–7 only. There were no effects in any of the selected organs that were weighed or examined grossly or histologically. Thus, the parental NOAEL was considered to be 1023 ppm, the highest dose tested. Using standard minute volume and bodyweight values for Sprague Dawley rats in a subchronic study, the calculated NOAEL was considered to be 1239 mg/kg/day (https://echa.europa.eu/registration-dossier/-/registered-dossier/10230/7/9/2 ECHA, 2012a).

Since the effects of an increase in urine cellularity and organ weight changes from the oral gavage study (Gaunt et al., 1972) were not seen in the OECD 421 inhalation study for both male and female rats, thus the NOAEL of 1087 mg/kg/day from the subchronic inhalation study of male Sprague Dawley rats was considered for the repeated dose toxicity endpoint. 100% inhaled dose was considered for calculating the NOAEL. **Therefore, the 2-undecanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-heptanone NOAEL in mg/kg/day by the total systemic exposure to 2-undecanone, 1087/0.0005 or 2174000.**

In addition, the total systemic exposure to 2-undecanone (0.5 μg/kg/day) is below the TTC (9 μg/kg/day) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: Johnson et al., 1978; Spencer et al., 1978; Misumi and Nagano, 1984.

Literature Search and Risk Assessment Completed On: 09/07/17.

10.1.5. Reproductive toxicity

The margin of exposure for 2-undecanone is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.6. Risk assessment

There is developmental toxicity data on 2-undecanone. In a developmental toxicity study, female pregnant Golden Syrian hamsters were administered test material 2-undecanone via oral gavage at doses of 0, 96, or 960 mg/kg/day from gestation days (GDs) 1–14. Observations included fetal and maternal body weights and full batteries of developmental parameters were monitored. Pregnant uteri were collected after laparotomy and the numbers of resorption and dead fetuses were recorded. Live fetuses were weighed and one-third of each litter was fixed in Bouin's fluid and subsequently sectioned in the mid-sagittal plane. Two-thirds of each litter were processed for skeletal examination. There was a significant decrease in maternal body weight at 960 mg/kg/day. There were no significant changes in any fetal parameter and no malformations were observed at either dose level. Thus, the NOAEL for maternal toxicity was considered to be 96 mg/kg/day. The NOAEL for developmental toxicity was considered to be 960 mg/kg/day (https://iaspub.epa.gov/oppthpv/document_api.download?FILE=Summaries_c15014rs.pdf, Whillhite, 1986).

Read-across material 2-heptanone (CAS # 110-43-0; see Section 5) has sufficient developmental toxicity data to support the developmental toxicity endpoint. In an OECD 414/GLP prenatal developmental toxicity study, 2-heptanone was administered via inhalation (whole-body) to groups of 25 female Crl:CD(SD) rats for 6 h/day from GDs 6 through 19, at target concentrations of 0 (filtered air), 300, 600, or 1200 ppm (actual measured concentrations of 0, 303, 613, or 1251 ppm). No test material–related macroscopic findings were observed in the dams and treatment did not affect intrauterine growth and survival. Examination of the fetuses revealed no external, visceral or skeletal malformations or developmental variations that could be attributed to the test material. Thus, the NOAEC for developmental toxicity was considered to be 1251 ppm, based on the lack of adverse developmental effects. The NOAEC for maternal toxicity was considered to be 613 ppm, due to decreased mean bodyweight gain, mean net bodyweight gain and food consumption. Using standard minute volume and body weights for female Sprague Dawley rats in a subchronic study, the calculated developmental toxicity NOAEL was considered to be 1547 mg/kg/day, the highest dose tested and the maternal toxicity was considered to be 758 mg/kg/day (https://echa.europa.eu/registration-dossier/-/registered-dossier/10230/7/9/3 ECHA, 2012a).

A pilot prenatal developmental toxicity study was summarized by the US EPA in their hazard assessment of 2-heptanone, but was not presented in the US EPA HPV submission. According to the US EPA, 2-heptanone was administered via oral gavage to pregnant Crj:CD(SD) rats (12–13/dose) at doses of 0, 100, 250, 500, or 1000 mg/kg/day in corn oil on GDs 6 to 15. Observations included mortality, clinical signs, body weight, and food consumption. The gravid uterine weights, number of corpora lutea, implantations, fetal survival, sex, and fetal weights were assessed. All fetuses were examined for external abnormalities, and half of the fetuses from each litter were examined for skeletal and visceral abnormalities. Ataxia was observed in dams treated at 500 and 1000 mg/kg/day. Furthermore, bradypnea, lacrimation, and prone position was observed at 1000 mg/kg/day. Maternal bodyweight gain was significantly decreased at 1000 mg/kg/day in the absence of changes in the mean body weight and food consumption. At 1000 mg/kg/day, live fetal body weight and the number of ossified sacrococcygeal vertebral bodies in males were significantly decreased. At 500 mg/kg/day, the sex ratio (male/alive) was significantly increased. There were no other treatment-related effects on the number of corpora lutea, implantations and live fetuses, sex ratio, embryo, and fetal mortality. No other effect on external, visceral, or skeletal anomalies or variations were observed. The NOAEL for maternal toxicity was considered to be 250 mg/kg/day, based on ataxic gait. The NOAEL for developmental toxicity was considered to be 500 mg/kg/day, based on effects on fetal body weight and skeletal ossification at the highest dose (US EPA, 1993). The most conservative NOAEL of 500 mg/kg/day was considered for the developmental toxicity endpoint. **Therefore, the 2-undecanone MOE for the developmental toxicity endpoint can be calculated by dividing the 2-heptanone NOAEL in mg/kg/day by the total systemic exposure to 2-undecanone, 500/0.0005 or 1000000.**

There are no fertility data on 2-undecanone. Read-across material, 2-heptanone (CAS # 110-43-0; see Section 5) has sufficient fertility data to support the fertility endpoint. In an OECD 421/GLP combined reproductive/developmental screening study, 2-heptanone was administered to groups of 12 Sprague Dawley rats/sex via inhalation at target concentrations of 0, 80, 400, or 1000 ppm (actual measured concentrations of 0, 79, 406, or 1023 ppm) for 6 h/day, 7 days/week during premating, mating, GD, and early lactation for a total of 50 exposure days for males and 34–47 exposure days for females. There were no effects in any of the reproductive organs that were weighed or examined grossly or histologically. There were no treatment-related effects on litter parameters or reproductive performance observed. No treatment-induced alterations in pup body weight, clinical signs, or external abnormalities were observed. Thus, the NOAEC for effects on fertility was considered to be 1023 ppm, the highest concentration tested. Using standard minute volume and bodyweight values for Sprague Dawley rats in a subchronic study, the calculated NOAEL for effects on fertility was considered to be 1239 mg/kg/day (https://echa.europa.eu/registration-dossier/-/registered-dossier/10230/7/9/2 ECHA, 2012a). 100% inhaled dose was considered for calculating the NOAEL. **Therefore, the 2-undecanone MOE for the fertility endpoint can be calculated by dividing the 2-heptanone NOAEL in mg/kg/day by the total systemic exposure to 2-undecanone, 1239/0.0005 or 2478000.**

In addition, the total systemic exposure to 2-undecanone (0.5 μg/kg/day) is below the TTC (9 μg/kg/day) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/07/17.

10.1.7. Skin sensitization

Based on the existing data and the read-across 2-heptanone (CAS # 110-43-0), 2-undecanone does not a safety concern for skin sensitization under the current, declared levels of use.

10.1.8. Risk assessment

Limited skin sensitization studies are available for 2-undecanone. Based on the read-across analog 2-heptanone (CAS # 110-43-0; see Section 5), 2-octanone does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical

structure of these materials indicate that they would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), read-across material 2-heptanone was found to be negative up to maximum tested concentration of 100%, which resulted in a Stimulation Index of 1.6 (https://echa.europa.eu/registration-dossier/-/registered-dossier/10230/7/5/2 ECHA, 2012a). In guinea pigs, an open epicutaneous test did not present reactions indicative of sensitization up to 2% 3-octanone and 4% read-across 2-heptanone (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with 5% 2-undecanone (3450 μg/cm^2) (RIFM, 1974a). Additionally, no skin sensitization reactions were observed with 4% read-across material 2-heptanone (2760 μg/cm^2) in a human maximization test (RIFM, 1974b).

Based on weight of evidence from structural analysis and human studies, and read-across 2-heptanone, 2-undecanone does not a safety concern for skin sensitization under the current, declared levels of use.

Additional References: Patel et al., 2002.

Literature Search and Risk Assessment Completed On: 08/28/17.

10.1.9. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra and available *in vivo* study data, 2-undecanone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

UV/Vis absorption spectra for 2-undecanone indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In an *in vivo* study conducted with hairless mice and mini-pigs, undiluted 2-Undecanone followed by UVA/UVB irradiation did not result in any phototoxic reactions (RIFM, 1974c). Based on lack of absorbance and the *in vivo* study data, 2-Undecanone does not present a concern for phototoxicity or photoallergenicity.

10.1.11. UV spectra analysis

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/22/17.

10.1.12. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 2-undecanone is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.13. Risk assessment

There are no inhalation data available on 2-undecanone. Based on the Creme RIFM model, the inhalation exposure is 0.0028 mg/day. This exposure is 167.9 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; #57336); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al., 2009; #57336, Cramer Class II materials default to Cramer Class III.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/25/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-undecanone was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (US EPA, 2012b) (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 2-Undecanone 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-undecanone 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 (#68218). As noted in the Criteria Document, the screening criteria applied are the same criteria used in the EU for REACH (ECHA, 2012b). For persistence, if the EPI Suite models BIOWIN 2 or BIOWIN 6 < 0.5 and BIOWIN 3 < 2.2, then the material is considered as 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. Should additional assessment be required, based on these model outputs (Step 1), a weight-of-evidence based review is 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., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on biodegradation, fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current VoU (2015), 2-undecanone presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. **RIFM, 1996:** 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 guidelines. The biodegradation rate after 28 days was 85.4%.

10.2.3.2. Ecotoxicity. No data available.

10.2.3.3. Other available data. 2-Undecanone has been registered under REACH with the additional data available:

A *Daphnia magna* acute toxicity study was conducted according to the OECD 202 method. The 48-h EC50 based on measured concentration (arithmetic mean) was reported to be 0.23 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 24-h EC10 was reported to be 0.79 mg/L.

10.2.3.4. Risk assessment refinement. Since 2-Undecanone has passed the screening criteria, measured data is reported for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	9.315			1,000,000	0.009315	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.213	2.797	3.978	10,000	0.2797	Neutral Organic SAR

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002; #40315)

Exposure	Europe	North America
Log K_{ow} used	3.69	3.69
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.2797 μg/L. The revised PEC/PNECs for EU and NA are < 1, and therefore, this material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 8/14/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/19.

12. Conflicts of interest

The authors declare that they have no conflicts of interest.

13. Declaration of interests

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110634.

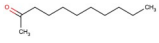
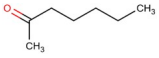
Appendix

Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite (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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material
Principal Name	2-Undecanone	2-Heptanone
CAS No.	112-12-9	110-43-0
Structure		
Similarity (Tanimoto Score)		0.67
Read-across Endpoint		• Genotoxicity • Repeated dose • Developmental and reproductive • Skin sensitization • Respiratory
Molecular Formula	$C_{11}H_{22}O$	$C_7H_{14}O$
Molecular Weight	170.30	114.19
Melting Point (°C, EPI Suite)	3.83	−42.77
Boiling Point (°C, EPI Suite)	224.03	141.64
Vapor Pressure (Pa @ 25°C, EPI Suite)	14.9	655
Log Kow (KOWWIN v1.68 in EPI Suite)	4.09	1.98
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	19.71	4300
J_{max} (μg/cm^2/h, SAM)	16.119	215.198
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.78E-004	1.54E-004
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)
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	• Not classified	• Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
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	• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
Local Respiratory Toxicity		
Respiratory Sensitization (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-undecanone (CAS # 112-12-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physicochemical properties and expert judgment, 2-heptanone (CAS # 110-43-0) was identified as read-across materials with sufficient data for toxicological evaluation.

14. Conclusions

- 2-Heptanone (CAS # 110-43-0) was used as a read-across analog for the target material 2-undecanone (CAS # 112-12-9) for the genotoxicity, repeated dose, developmental and reproductive, skin sensitization and respiratory endpoints.
  - The target substance and the read-across analog are structurally similar and belong to the class of ketones.
  - The target substance and the read-across analog share a common saturated aliphatic ketone fragment.
  - The key difference between the target substance and the read-across analog is that the target has a C11 aliphatic chain, while the read-across analog has a C7 aliphatic chain. This structural difference is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by a common saturated aliphatic ketone fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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