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Short Review

RIFM fragrance ingredient safety assessment, undecane, CAS Registry Number 1120-21-4

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ARTICLE INFO

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Phototoxicity/photoallergenicity
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Environmental safety

Version: 041620. This version replaces any previous versions.
Name: Undecane CAS Registry Number: 1120-21-4

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

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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, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test

TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Undecane was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog nonane (CAS # 111-84-2) show that undecane is not expected to be genotoxic. Data on undecane provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Based on existing data and the application of the Dermal Sensitization Threshold (DST), undecane does not present a safety concern for skin sensitization under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; undecane is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to undecane is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; undecane 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., PEC/PNEC [Predicted Environmental Concentration/Predicted No Effect Concentration]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(JECDB, 1996; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 100 mg/kg/day.	JECDB (1996)
Reproductive Toxicity: Developmental toxicity: NOAEL = 300 mg/kg/day. Fertility: NOAEL = 1000 mg/kg/day.	JECDB (1996)
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC is available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Screening-level: 3.45 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 120.9 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 0.1175 mg/L	(RIFM Framework; Salvito et al., 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 et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 0.1175 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.0001175 μg/L	
•**Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Undecane
2. **CAS Registry Number**: 1120-21-4
3. **Synonyms**: Undecane
4. **Molecular Formula**: $C_{11}H_{24}$
5. **Molecular Weight**: 156.31
6. **RIFM Number**: 6520
7. **Stereochemistry**: No stereocenters or stereoisomers possible.

2. Physical data

1. **Boiling Point:** 185.61 °C (EPI Suite)
2. **Flash Point:** 140.00 °F TCC (60.00 °C)*
3. **Log K_{OW}:** 5.74 (EPI Suite)
4. **Melting Point**: 32.36 °C (EPI Suite)
5. **Water Solubility:** 0.2571 mg/L (EPI Suite)
6. **Specific Gravity:** 0.74000 @ 25.00 °C*
7. **Vapor Pressure:** 0.436 mm Hg @ 20 °C (EPI Suite v4.0), 0.629 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** colorless clear liquid*

* http://www.thegoodscentscompany.com/data/rw1040461.html, retrieved on 03/25/15.

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. 95th Percentile Concentration in Hydroalcoholics: 0.00% (RIFM, 2016)
2. Inhalation Exposure*: 0.0048 mg/kg/day or 0.388 mg/day (RIFM, 2016)
3. Total Systemic Exposure**: 0.0051 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., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** Nonane (CAS # 111-84-2)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

8. Natural occurrence (discrete chemical) or Composition (NCS)

Undecane is reported to occur in the following foods by the VCF*:

Asafoetida oil
Citrus fruits
Dill (*Anethum* species)
Eucalyptus oil (*Eucalyptus globulus* Labill)
Laurel (*Laurus nobilis* L.)
Mastic (*Pistacia lentiscus*)
Milk and milk products
Pistachio oil (*Pistacia vera*)
Pistacia palaestina (*Pistacia terebinthus* L.)
Turpentine oil (*Pistacia terebinthus*)

*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. This is a partial list.

9. Reach dossier

Available; accessed 04/16/20.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, undecane does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of undecane 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with undecane in acetone 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 (JECDB, 1996). Under the conditions of the study, undecane was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of undecane; however, read-across can be made to nonane (CAS # 111-84-2; see Section VI).

The clastogenic activity of nonane 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 nonane in acetone at concentrations up to 1282.6 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 320 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Nonane did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, nonane was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, undecane and read-across material nonane do not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/13/19.

11.1.2. Repeated Dose Toxicity

The MOE for undecane is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient data on undecane to support the repeated dose toxicity endpoint. In an OECD 422 and GLP compliant study, 12 Crj:CD(SD) rats/sex/dose were orally administered undecane at doses of 0, 100, 300, or 1000 mg/kg/day for 46–53 days. Starting 2 weeks prior to mating, treatment duration was a total of 46 days in males and 53 days in females. No treatment-related mortality

was reported during the study. Increased salivation was reported in the high-dose group (both sexes) and mid-dose group (1 rat/sex). Food consumption in high-dose males decreased during the first half of the treatment but was higher than the controls during the second half of the treatment. However, in high-dose females, food consumption increased only during the second half of pregnancy and lactation. Despite the increase in food consumption in the latter half of treatment, bodyweight gain in high-dose males was significantly lower than controls. Biochemical changes included a significant decrease in albumin and glucose levels and increases in GTP, cholinesterase, total cholesterol, and α2-globulin in high-dose males. Alterations of hematology, clinical chemistry, and organ weight changes were reported in the high-dose group but were not considered to be of toxicological significance since there were no correlating histopathological changes. In addition, the increase in relative organ weights was attributed to decreased bodyweight gain in high-dose males. Thus, based on the decrease in male bodyweight gain at 1000 mg/kg/day dose, the NOAEL for this study was determined to be 300 mg/kg/day (JECDB, 1996).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 300/3 or 100 mg/kg/day.

Therefore, the MOE for undecane can be calculated by dividing the undecane NOAEL in mg/kg/day by total systemic exposure in mg/kg/day, to be 100/0.0051 or 19608.

In addition, the total systemic exposure for undecane (5.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: OECD, 2010; OECD, 2012; VanDuuren and Goldschmidt, 1976; Kim et al., 2006a; Kim et al., 2006b.

Literature Search and Risk Assessment Completed On: 10/07/19.

11.1.3. Reproductive Toxicity

The MOE for undecane is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on undecane that can be used to support the reproductive toxicity endpoint. In an OECD 422/GLP study, groups of 12 Crj: CD(SD) rats/sex/dose were administered undecane via oral gavage at doses of 0, 100, 300, or 1000 mg/kg/day in olive oil. Males were dosed for 46 days (14 days prior to mating until the end of the mating period), while females were dosed 14 days prior to mating until day 3 of lactation. In addition to systemic toxicity parameters, the reproductive toxicity parameters were also assessed. There were no treatment-related adverse effects on the sex cycle of females, copulation and conception of animals, or on any reproductive parameters reported up to the highest dose tested. There was a statistically significant decrease in bodyweight gain among the high-dose group male and female pups, but body weight was only decreased slightly (not significant) when compared to the control group. There were no effects observed in the viability, general condition, or macroscopic examination of pups. The authors of the study report concluded the reproductive and developmental toxicity NOEL to be 300 mg/kg/day, based on decreased bodyweight gain among the high-dose group pups. Since there were no observed effects on fertility, the NOAEL for fertility was considered to be 1000 mg/kg/day, the highest dose tested. Though there were no effects on the viability, general condition, and body weight of pups, the more conservative NOAEL of 300 mg/kg/day was considered for developmental toxicity, based on decreased bodyweight gain of the high-dose group pups (JECDB, 1996; OECD, 2012; ECHA, 2010).

The undecane MOE for the developmental toxicity endpoint can be calculated by dividing the undecane NOAEL in mg/kg/day by the total systemic exposure to undecane, 300/0.0051, or 58824.

The undecane MOE for the fertility endpoint can be calculated by dividing the undecane NOAEL in mg/kg/day by the total systemic exposure to undecane, 1000/0.0051, or 196078.

In addition, the total systemic exposure to undecane (5.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/13/19.

11.1.4. Skin sensitization

Based on existing data and the application of DST, undecane does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for undecane. No predictive tests in animals or confirmatory studies in humans exist for this material. Due to the absence of data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for nonane that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/09/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, undecane would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity data available for undecane. 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 et al., 2009). Based on the lack of absorbance, undecane does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/09/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for undecane is below the Cramer Class I TTC value for inhalation exposure local effects.

Table 1
Maximum acceptable concentrations for undecane that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	1.8×10^{-7}%
2	Products applied to the axillae	0.021%	7.5×10^{-6}%
3	Products applied to the face using fingertips	0.41%	2.7×10^{-8}%
4	Fine fragrance products	0.39%	6.1×10^{-5}%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	4.6×10^{-6}%
6	Products with oral and lip exposure	0.23%	NRU[2]
7	Products applied to the hair with some hand contact	0.79%	NRU[2]
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0075%
10	Household care products with mostly hand contact	2.7%	2.9×10^{-6}%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	6.3×10^{-6}%

Note: [a]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).
[b]No reported use.
[c]Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.6.1. Risk assessment. There are no inhalation data available on undecane. Based on the Creme RIFM Model, the inhalation exposure is 0.388 mg/day. This exposure is 3.61 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/15/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of undecane was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional volume of use, log Kow and molecular weight are needed to estimate a conservative risk quotient (RQ) expressed as the ratio: Predicted Environmental Concentration/Predicted No Effect Concentration (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). In Tier 2, the model ECOSAR (US EPA, 2012b; providing chemical class-specific ecotoxicity estimates) is used allowing for a lower uncertainty factor to be applied to the PNEC. 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 of the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated based on the actual regional tonnage and not the extremes of the range. Following the RIFM Environmental Framework, undecane was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify undecane as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same criteria used in the EU for REACH (ECHA, 2012). 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 an 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., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on current VoU (2015), undecane does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.3.3. Other available data. Undecane has been registered under REACH, and no additional data is available at this time.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.74	5.74
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0001175 μg/L. The revised PEC/PNECs for EU

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.1175			1,000,000	0.0001175	

and NA are not applicable. The material was cleared at screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 06/10/19.

12. Literature Search*

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

  Search keywords: CAS number and/or material names

  *Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 08/07/20.

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.2020.111745.

Appendix

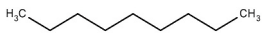
Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance 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).

	Target Material	Read-across Material
Principal Name	Undecane	Nonane
CAS No.	1120-21-4	111-84-2
Structure		
Similarity (Tanimoto Score)		1.00
Read-across Endpoint		• Genotoxicity
Molecular Formula	$C_{11}H_{24}$	C_9H_{20}
Molecular Weight	156.31	128.25
Melting Point (°C, EPI Suite)	−25.60	−53.50
Boiling Point (°C, EPI Suite)	195.90	150.80
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.49E+01	5.93E+02
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.74	5.65
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.40E-03	0.22
J_{max} (μg/cm^2/h, SAM)	0.001	0.050
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.96E+05	3.45E+05
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	• Not classified	• Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on undecane (CAS # 1120-21-4). 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, nonane (CAS # 111-84-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Nonane (CAS # 111-84-2) was used as a read-across analog for the target material undecane (CAS # 1120-21-4) for the genotoxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to a class of straight-chain saturated alkanes.
  - The target substance and the read-across analog share a straight hydrocarbon chain.
  - The key difference between the target substance and the read-across analog is that the target substance is 2 carbons longer in chain length than the read-across analog. This structural difference is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog do not have toxicity alerts. Data are consistent with *in silico* alerts.
  - 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.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

ECHA, 2010. REACH Registration Dossier: Decane. https://echa.europa.eu/lt/registration-dossier/-/registered-dossier/13896/1.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2016. Read-across Assessment Framework (RAAF). www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Japan Existing Chemical Data Base (JECDB), 1996. Undecane: Combined Repeated Dose Toxicity Study with the Reproduction/developmental Toxicity Screening Test.

Unpublished. Online Publication. http://dra4.nihs.go.jp/mhlw_data/home/file/file1120-21-4.html.
Kim, D., Andersen, M.E., Nylander-French, L.A., 2006a. Estimation of human skin permeability coefficients of jet fuel components in vivo. Toxicologist 90 (1), 170.
Kim, D., Andersen, M.E., Nylander-French, L.A., 2006b. Dermal absorption and penetration of jet fuel components in humans. Toxicol. Lett. 165 (1), 11–21.
Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.
Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.
OECD, 2010. SIDS Initial Assessment Profile: N-Undecane. https://hpvchemicals.oecd.org/UI/handler.axd?id=f46bca58-5272-4854-a33a-42128cd4013a.
OECD, 2012. SIDS Initial Assessment Profile: C9-C14 Aliphatic [≤2% Aromatic] Hydrocarbon Solvents Category. https://hpvchemicals.oecd.org/UI/handler.axd?id=51027239-af98-4b96-b936-aabea00b3fea.
OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing And Assessment (IATA)*. ENV/JM/HA(2015)7. http://www.oecd.org/.
OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. http://www.qsartoolbox.org/.
RIFM (Research Institute for Fragrance Materials, Inc), 2000. p-Anisyl Acetate: Acute Immobilisation Test (48h) to Daphnia Magna STRAUS. Unpublished Report from Symrise. RIFM Report Number 57389 (RIFM, Woodcliff Lake, NJ, USA.).
RIFM (Research Institute for Fragrance Materials, Inc), 2014. Nonane: Micronucleus Test in Human Lymphocytes in Vitro. RIFM Report Number 68214 (RIFM, Woodcliff Lake, NJ, USA.).
RIFM (Research Institute for Fragrance Materials, Inc), 2016. Exposure Survey 10, March 2016.
Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015a. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.
Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015b. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.
Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
VanDuuren, B.L., Goldschmidt, B.M., 1976. Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. J. Natl. Cancer Inst. 56 (6), 1237–1242.