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Short Review

RIFM fragrance ingredient safety assessment, dodecane, CAS Registry Number 112-40-3

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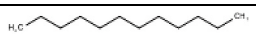
A B S T R A C T

Dodecane 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 dodecane is not expected to be genotoxic. Data on read-across analog undecane (CAS # 1120-21-4) provide a calculated Margin of Exposure (MOE) >100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/vis) spectra; dodecane 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 dodecane is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; dodecane 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.

Version: 050319. This version replaces any previous versions.



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Name: Dodecane CAS Registry Number: 112-40-3

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
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, 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.

Dodecane 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 dodecane is not expected to be genotoxic. Data on read-across analog undecane (CAS # 1120-21-4) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/vis) spectra; dodecane 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 dodecane is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; dodecane 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.	(Zeiger, 1992; RIFM, 2014a)
Repeated Dose Toxicity: NOAEL = 300 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 available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Screening-level: 3.41 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 207.7 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia* LC50: 0.018 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia* LC50: 0.018 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0018 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** Dodecane
2. **CAS Registry Number**: 112-40-3
3. **Synonyms**: アルカン(C = 10–29); Dodecane
4. **Molecular Formula**: $C_{12}H_{26}$
5. **Molecular Weight**: 170.34
6. **RIFM Number**: 5147
7. **Stereochemistry**: No stereocenters present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 205.71 °C (EPI Suite)
2. **Flash Point:** 70 °C (Globally Harmonized System)
3. **Log K_{OW}**: 6.23 (EPI Suite)
4. **Melting Point**: 20.85 °C (EPI Suite)
5. **Water Solubility:** 0.1099 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.16 mm Hg @ 20 °C (EPI Suite v4.0), 0.236 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} · cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

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

1. 95th Percentile Concentration in Hydroalcoholics: 0.0049% (RIFM, 2016)
2. Inhalation Exposure*: 0.0000019 mg/kg/day or 0.00014 mg/day (RIFM, 2016)
3. Total Systemic Exposure**: 0.00075 mg/kg/day (RIFM, 2016)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford et al., 2015a; Safford, 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, 2015a, 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:** Undecane (CAS # 1120-21-4)
   c. **Reproductive Toxicity:** Undecane (CAS # 1120-21-4)
   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

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

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

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

Allium species
Asafoetida oil
Cocoa category
Coconut (*Cocos nucifera* L.)
Eucalyptus oil (*Eucalyptus globulus* Labill)
Licorice (*Glycyrrhiza* species)
Milk and milk products
Mustard (*Brassica* species)
Passion fruit (*Passiflora* species)
Tea

*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 05/03/19.

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, dodecane does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. Dodecane was assessed in the BlueScreen assay and found positive for cytotoxicity without metabolic activation (positive: <80% relative cell density) and negative for genotoxicity with and without metabolic activation (RIFM, 2014b). 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 data assessing the mutagenic and clastogenic activity of dodecane; however, read-across can be made to nonane (CAS # 111-84-2; see Section VI).

The mutagenic activity of nonane has been evaluated in a bacterial reverse mutation assay conducted following methods equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, TA104, and TA102 were treated with nonane in dimethyl sulfoxide (DMSO) at concentrations up to 10000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Zeiger, 1992). Under the conditions of the study, nonane was not mutagenic in the Ames test, and this can be extended to dodecane.

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, 2014a). Under the conditions of the study, nonane was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to dodecane.

Based on the data available, nonane does not present a concern for genotoxic potential, and this can be extended to dodecane.

Additional References: None.

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

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no data on dodecane to support the repeated dose toxicity endpoint. Read-across material undecane (CAS 1120-21-4; see Section VI), has sufficient data to support 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 bw/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, the 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 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 dodecane can be calculated by dividing the undecane NOAEL in mg/kg/day by total systemic exposure to dodecane in mg/kg/day, to be 100/0.00075, or 133333.

In addition, the total systemic exposure for dodecane (0.75 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 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 (1976); Kim (2006a); Kim (2006b).

Literature Search and Risk Assessment Completed On: 06/11/19.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on dodecane. Read-across material undecane (CAS # 1120-21-4; see Section VI) has sufficient reproductive toxicity data 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 dodecane MOE for the developmental toxicity endpoint can be calculated by dividing the undecane NOAEL in mg/kg/day by the total systemic exposure to dodecane, 300/0.00075, or 400000.

The dodecane MOE for the fertility endpoint can be calculated by dividing the undecane NOAEL in mg/kg/day by the total systemic exposure to dodecane, 1000/0.00075, or 1333333.

In addition, the total systemic exposure to dodecane (0.75 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 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, dodecane 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, 2007; Toxtree v3.1.0; OECD toolbox v4.2). No predictive skin sensitization studies are available for dodecane. Due to the lack of data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). 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 dodecane 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: 06/03/19.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for dodecane in experimental models. UV/Vis spectra 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, 2009). Based on the lack of absorbance, dodecane does not present a concern for phototoxicity or photoallergenicity.

Table 1
Maximum acceptable concentrations for dodecane 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%	NRU[b]
2	Products applied to the axillae	0.021%	NRU[b]
3	Products applied to the face using fingertips	0.41%	NRU[b]
4	Fine fragrance products	0.39%	NRU[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.020%
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	0.26%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	NRU[b]
10	Household care products with mostly hand contact	2.7%	NRU[b]
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	1.1%

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.

11.1.5.2. UV spectra analysis. UV/Vis 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 $mol^{-1} \cdot cm^{-1}$ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/08/19.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on dodecane. Based on the Creme RIFM Model, the inhalation exposure is 0.00014 mg/day. This exposure is 10000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Nilsen (1988); Gerarde (1963).

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 dodecane was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, dodecane 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 dodecane as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF 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), dodecane presents 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.

11.2.4. Other available data

Dodecane has been registered for REACH with no additional data available at this time.

11.2.4.1. 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 Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	6.23	6.23
Biodegradation Factor Used	1	1
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 additional assessment is necessary.

The RIFM PNEC is 0.0018 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 Volume of Use.

Literature Search and Risk Assessment Completed On: 06/11/19.

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=DetailQueryResults&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 09/30/19.

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.2020.111759.

Appendix

Read-across Justification

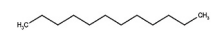
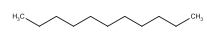
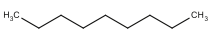
Methods

The read-across analogs were 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.

	(Fish) (mg/L)	(*Daphnia*) (mg/L)	(mg/L)			
RIFM Framework Screening-level **(Tier 1)**	0.048			1,000,000	0.00048	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.022	0.018	0.069	10,000	0.0018	Neutral Organics

- 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).
- Jmax 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	Read-across Material
Principal Name	Dodecane	Undecane	Nonane
CAS No.	112-40-3	1120-21-4	111-84-2
Structure			
Similarity (Tanimoto Score)		1.00	1.00
Read-across Endpoint		• Repeated Dose Toxicity • Reproductive Toxicity	• Genotoxicity
Molecular Formula	$C_{12}H_{26}$	$C_{11}H_{24}$	C_9H_{20}
Molecular Weight	170.34	156.31	128.25
Melting Point (°C, EPI Suite)	−9.60	−25.60	−53.50
Boiling Point (°C, EPI Suite)	216.30	195.90	150.80
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.80E+01	5.49E+01	5.93E+02
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	6.10	5.74	5.65
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.70E-03	4.40E-03	0.22
J_{max} (μg/cm^2/h, SAM)	0.001	0.001	0.050
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	8.29E+05	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
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Perhexiline (Hepatotoxicity) Alert	• Not categorized	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)	
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

Summary

There are insufficient toxicity data on dodecane (CAS # 112-40-3-). 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, read-across materials undecane (CAS # 1120-21-4) and nonane (CAS # 111-84-2) were identified as analogs with sufficient data for toxicological evaluation.

Conclusions

- Undecane (CAS # 1120-21-4) was used as a read-across analog for the target material dodecane (CAS # 112-40-3-). for the repeated dose and reproductive endpoints.
  - 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 nonane as a common substructure.
  - The key difference between the target substance and the read-across analog is that the target substance is 1 carbon longer in chain length compared to 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 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 material has a Perhexiline (Hepatotoxicity) Alert for the Repeated Dose (HESS) characterization scheme. However, this alert only applies for compounds such as perhexiline, 4,4′-diethylaminoethoxyhexestrol, or amiodarone. Dodecane is not part of the training set for this alert, and therefore, the predictions are superseded by data.
- 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.

- Nonane (CAS # 111-84-2) was used as a read-across analog for the target material dodecane (CAS # 112-40-3-) 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 nonane as a common substructure.
  - The key difference between the target substance and the read-across analog is that the target substance is 3 carbons longer in chain length compared to 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 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 does 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.

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