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Short Review

RIFM fragrance ingredient safety assessment, nonane, CAS Registry Number 111-84-2

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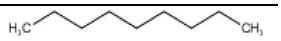
ARTICLE INFO

Keywords:
Genotoxicity
Repeated dose, developmental, and reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

Version: 050319. This version replaces any previous versions.
Name: Nonane
CAS Registry Number: 111-84-2



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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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(*continued*)

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.

Nonane was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that nonane is not genotoxic. Data on read-across analog decane (CAS # 124-18-5) 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), nonane does not present a safety concern for skin sensitization under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; nonane 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 nonane is below the TTC (1.4 mg/day). For the hazard assessment based on the screening data, nonane is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, nonane was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (Zeiger, 1992; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day. (ECHA REACH Dossier: Decane; ECHA, 2010)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day. OECD (2011)
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: 3.51 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 104.9 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Not applicable
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; no Volume of Use in 2015 reported for Europe and North America

1. Identification

1. Chemical Name: Nonane
2. CAS Registry Number: 111-84-2
3. Synonyms: Nonane
4. Molecular Formula: C_9H_{20}
5. Molecular Weight: 128.25
6. RIFM Number: 5146
7. Stereochemistry: No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 142.69 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 4.76 (EPI Suite)
4. **Melting Point**: −56.16 °C (EPI Suite)
5. **Water Solubility:** 0.4058 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 3.63 mm Hg @ 20 °C (EPI Suite v4.0), 4.96 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:** Not Available

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. 95th Percentile Concentration in Hydroalcoholics: 0.00029% (RIFM, 2018)
2. Inhalation Exposure*: 0.0000001 mg/kg/day or 0.000004 mg/day (RIFM, 2018)
3. Total Systemic Exposure**: 0.000023 mg/kg/day (RIFM, 2018)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015a, 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: None
   b. Repeated Dose Toxicity: Decane (CAS # 124-18-5)
   c. Reproductive Toxicity: Decane (CAS # 124-18-5)
   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.
Additional References: None.

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

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

Annatto (*Bixa orellana* L.)	Citrus fruits
Chicken	Egg
Guinea hen	Milk and milk products
Honey	Passion fruit (*Passiflora* species)
Laurel (*Laurus nobilis* L.)	Pistacia palaestina (*Pistacia terebinthus* L.)

*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 (ECHA, 2011).

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, nonane does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Nonane was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2016). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

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.

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, nonane does 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 nonane is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient data for nonane to support the repeated dose toxicity endpoint. Although subchronic studies are available for the target material (ECHA, 2011), these studies lack in robust experimental design and study reporting. Hence, these studies have been deemed as insufficient and used as Weight of Evidence only in this risk assessment. Read-across material decane (CAS # 124-18-5, see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

In an OECD 422 gavage study, 10 Sprague Dawley rats/sex/day were orally administered decane at doses of 25, 150, and 1000 mg/kg/day

through oral gavage for 28 days. There were no significant treatment-related effects at any dose level. The NOAEL for this study was considered to be 1000 mg/kg/day (ECHA, 2010). In another 28-day inhalation study on groups of 5 Sprague Dawley rats/sex/dose, animals were exposed to decane via whole-body inhalation at doses of 75, 300, and 1200 mg/kg/day. No treatment-related adverse effects were reported with an exception of extensive vacuolization and atrophy of the seminiferous tubules in 3 male rats receiving the highest dose. Male rats in the low- and mid-dose groups were also reported to have this effect but with less severity. However, the authors were unable to identify the toxicological significance of this effect as the study did not test for reproductive parameters. Since no other treatment-related adverse effects were reported, the NOAEL for this study was considered to be 1200 mg/kg/day (Rim, 2004). The most conservative NOAEL of 1000 mg/kg/day from the OECD 422 study was used for the repeated dose toxicity endpoint in this safety assessment.

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 studies. The safety factor has been approved by the Expert Panel for Fragrance Safety*. Thus, the derived NOAEL for repeated dose toxicity data is 1,000 mg/kg/day/3 or 333.33 mg/kg/day.

Therefore, the nonane MOE for the repeated dose toxicity endpoint can be calculated by dividing the NOAEL for decane in mg/kg/day by the total systemic exposure to nonane, 333.33/0.000023 or 14492609.

In addition, the total systemic exposure to nonane (0.023 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*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: None.

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

11.1.3. Reproductive toxicity

The MOE for nonane 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 nonane. Read-across material decane (CAS # 124-18-5; 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 10 Sprague Dawley rats/sex/dose were administered Linpar 10 (commercial decane; composition 97% 1-decane) via oral gavage at doses of 0, 25, 150, or 1000 mg/kg/day in 0.5% methylcellulose. Males were dosed 14 days prior to mating and continued to the end of mating, while females were dosed 14 days prior to mating to day 4 of lactation. In addition to systemic toxicity parameters, reproductive performance, offspring survival, and litter data were also evaluated. Reproductive assessment also included reproductive organ weight determination and gross and histopathological examination of the reproductive tract (emphasis on stages of spermatogenesis in male gonads and interstitial testicular cell structure). No treatment-related adverse effects on the reproductive parameters and on the development of pups were observed. Thus, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (OECD, 2011). **Therefore, the nonane MOE for the reproductive toxicity endpoint can be calculated by dividing the decane NOAEL in mg/kg/day by the total systemic exposure to nonane, 1000/0.000023 or 43478261.**

In addition, the total systemic exposure to nonane (0.023 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: 06/12/19.

11.1.4. Skin sensitization

Based on existing data and the application of DST, nonane 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 v 4.3). No predictive skin sensitization studies are available for nonane. Due to the absence 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 nonane

Table 1
Maximum acceptable concentrations for nonane 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%	1.2×10^{-5}
2	Products applied to the axillae	0.021%	8.4×10^{-5}
3	Products applied to the face using fingertips	0.41%	8.4×10^{-6}
4	Fine fragrance products	0.39%	2.8×10^{-4}
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	2.9×10^{-5}
6	Products with oral and lip exposure	0.23%	5.2×10^{-5}
7	Products applied to the hair with some hand contact	0.79%	1.7×10^{-5}
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0019
10	Household care products with mostly hand contact	2.7%	NRU[2]
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	NRU[2]

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

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 spectra, nonane 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 nonane in experimental models. UV/Vis absorption 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, nonane does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

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

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to lack of appropriate data. The exposure level for nonane 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 nonane. Based on the Creme RIFM Model, the inhalation exposure is 0.000004 mg/day. This exposure is 350000 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).bib_Nilsen_et_al_1988

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 nonane 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, nonane was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify nonane 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 $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

Risk Assessment: Not applicable.

11.2.2. Key studies

Biodegradation: No data available.

Ecotoxicity: No data available.

11.2.2.1. Other available data. Nonane has been registered for REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

Not applicable.

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 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.2020.111608.

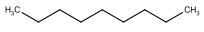
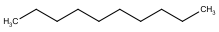
Appendix

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.
- 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	Nonane	Decane
CAS No.	111-84-2	124-18-5
Structure		
Similarity (Tanimoto Score)		1.00
Read-across Endpoint		• Repeated Dose Toxicity • Reproductive Toxicity
Molecular Formula	C_9H_{20}	$C_{10}H_{22}$
Molecular Weight	128.25	142.28
Melting Point (°C, EPI Suite)	−53.50	−29.70
Boiling Point (°C, EPI Suite)	150.80	174.10
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.93E+02	1.91E+02
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.65	5.01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.22	0.052
J_{max} (μg/cm^2/h, SAM)	0.050	0.011
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.45E+05	5.22E+05
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• 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

Summary

There are insufficient toxicity data on nonane (CAS # 111-84-2). 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 analog decane (CAS # 124-18-5) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Decane (CAS # 124-18-5) was used as a read-across analog for the target material nonane (CAS # 111-84-2) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to a class of saturated alkanes.
  - o The target substance and the read-across analog share straight chain alkane structures.
  - o The key difference between the target substance and the read-across analog is that the target substance is 1 carbon shorter than the read-across analog. This structural difference is toxicologically insignificant.
  - o 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.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog do not have any toxicity alerts. Data are consistent with *in silico* alerts.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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. Retrieved from. https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/13896.

ECHA, 2011. REACH registration dossier: nonane. Retrieved from. https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/11446.

ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. Read-across assessment framework (RAAF). Retrieved from. 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.

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.

Nilsen, O.G., Haugen, O.A., Zahlsen, K., Halgunset, J., Helseth, A., Aarset, H., Eide, I., 1988. Toxicity of n-C9 to n-C13 alkanes in the rat on short term inhalation. Pharmacol. Toxicol. 62 (5), 259–266.

OECD, 2011. SIDS initial assessment profile. Retrieved from. https://hpvchemicals.oecd.org/UI/handler.axd?id=6fd5985f-8783-4dda-ac59-a3c2e913d576.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

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. Report on the Testing of Nonane in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69789.

RIFM (Research Institute for Fragrance Materials, Inc), 2018. Exposure survey, 22. November 2018.

Rim, K.T., Kim, H.Y., Song, K.S., Chung, Y.H., Chang, H.K., Han, J.H., Lee, S.B., Chun, Y.S., Lee, Y.M., Yu, I.J., 2004. A twenty-eight days inhalation toxicity study of n-decane in Sprague Dawley rats. Environmental Health and Toxiology (EHT). 19 (4), 345–352.

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.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Mol. Mutagen. 19 (Suppl. 21), 2–141.