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Short Review

RIFM fragrance ingredient safety assessment, nonanoic acid, CAS Registry Number 112-05-0

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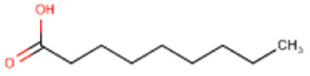
Version: 043019. This version replaces any previous versions.

Name: Nonanoic acid CAS Registry Number: 112-05-0



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., 2015, 2017compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding

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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

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Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

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

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

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

Nonanoic acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that nonanoic acid is not genotoxic and provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on the target material and read-across analog octanoic acid (CAS # 124-07-2) provide a calculated MOE >100 for the developmental toxicity endpoint. Data on analog octanoic acid (CAS # 124-07-2) provide a calculated MOE >100 for the fertility endpoint. Data from analogs octanoic acid (CAS # 124-07-2) and heptanoic acid (CAS # 111-14-8) show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; nonanoic acid is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for Cramer Class I; exposure is below the TTC (1.4 mg/day). For the environmental endpoints, nonanoic acid was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on current VoU in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2014; ECHA REACH Dossier: Nonanoic Acid; ECHA, 2011a)
Repeated Dose Toxicity: NOAEL = 333.33 mg/kg/day.	(ECHA REACH Dossier: Nonanoic Acid; ECHA, 2011a)
Reproductive Toxicity: Developmental toxicity: 1500 mg/kg/day. Fertility: NOAEL = 1000 mg/kg/day.	(ECHA REACH Dossier: Nonanoic Acid; ECHA, 2011a; JECDB, 2013)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(ECHA REACH Dossier: Octanoic Acid; ECHA, 2011b; Basketter et al., 1998)
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:

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Critical Measured Value: 68–75% (OECD 301 B)	(ECHA REACH Dossier: Nonanoic Acid; ECHA, 2011a)
Bioaccumulation:	
Screening-level: 3.162 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 10.16 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: 10.16 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.01016 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Nonanoic acid
2. **CAS Registry Number:** 112-05-0
3. **Synonyms:** Nonylic acid; Pelargonic acid; Pergonic acid; 1-Octanecarboxylic acid; Nonoic acid; Pelargic acid; ｱﾙｶﾝ酸(C = 4~30); Nonanoic acid
4. **Molecular Formula:** $C_9H_{18}O_2$
5. **Molecular Weight:** 158.24
6. **RIFM Number:** 820
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 268 °C (FMA), 262.36 °C (EPI Suite)
2. **Flash Point:** 137 °C (GHS), >200 °F; CC (FMA)
3. **Log K_{OW}:** 3.52 (EPI Suite)
4. **Melting Point**: 9 °C (FMA), 11.3 °C (EOA, 1976 Sample 76–223), 59.08 °C (EPI Suite)
5. **Water Solubility:** 207.8 mg/L (EPI Suite)
6. **Specific Gravity:** 0.904 (FMA), 0.9206 (EOA, 1976 Sample 76–223)
7. **Vapor Pressure:** 0.0134 mm Hg @ 20 °C (EPI Suite v4.0), 0.0214 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:** Oily colorless liquid with fatty odor, crystallizes when cooled, mildly nut-like fatty and acid odor taste is quite powerful, waxy nut-like in extreme dilution, not sour but slightly brandy-like (Arctander, Volume II, 1969)

3. Volume of use (Worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00054% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.0000011 mg/kg/day or 0.000077 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.000046 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015, 2017; Safford et al., 2015, 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
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2 .Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** Octanoic acid (CAS # 124-07-2)
   d. **Skin Sensitization:** Octanoic acid (CAS # 124-07-2); heptanoic acid (CAS # 111-14-8)
   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.

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

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

Acerola (*Malpighia*)
Beer
Cashew Apple (*Anacardium occidentale*)
Citrus Fruits
Honey
Loquat (*Eriobotrya japonica* Lindl.)
Malt
Milk and Milk Products
Vinegar
Whiskey

*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 04/02/19 (ECHA, 2011a).

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, nonanoic acid does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Nonanoic acid was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of nonanoic acid 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 nonanoic acid in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2011a). Under the conditions of the study, nonanoic acid was not mutagenic in the Ames test.

The clastogenic activity of nonanoic acid 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 nonanoic acid in DMSO at concentrations up to 1585 μg/mL in a DRF study. Micronuclei analysis was conducted at 770 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. In the 3-h treatment in the presence of S9, significant increases in the binucleate cells with micronuclei (BNMN) frequencies as compared to the concurrent vehicle control were observed at the top evaluated dose (610 μg/mL). However, this increase was considered to be biologically irrelevant as the BNMN frequency observed at this dose level (1.55%) was within the historical vehicle control range. No statistically significant increase in the BNMN frequencies was observed at any other evaluated concentrations in any treatment condition with or without S9 (RIFM, 2014). Under the conditions of the study, nonanoic acid was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, nonanoic acid does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/15/19.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on nonanoic acid. An OECD 407 and GLP-compliant subchronic toxicity study was conducted on 5 Wistar rats/sex/dose. Animals were administered nonanoic acid (purity: 93%) through gavage at doses of 0 (vehicle: propylene glycol), 50, 150, and 1000 mg/kg/day for 28 days. No treatment-related mortality or adverse effects were reported for any of the tested parameters up to the highest tested dose. Although forestomach anomalies were reported in the high-dose group, these effects

were not considered relevant to human health due to anatomical differences between the 2 species. Therefore, the no observed adverse effect level (NOAEL) for repeated dose toxicity was considered to be 1000 mg/kg/day (ECHA, 2011a; Health Canada, 2017).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day study. The safety factor has been approved by the Expert Panel for Fragrance Safety*. **Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3, or 333.3 mg/kg/day.**

Therefore the MOE can be calculated by dividing the NOAEL for nonanoic acid by the total systemic exposure (in mg/kg/day), 333.33/0.000046 or 7246304.

In addition, the total systemic exposure to nonanoic acid (0.046 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 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: https://rifmdatabase.rifm.org/rifmweb/material/1046601/publicationsFCT, 1978; HSDB, 2008.

Literature Search and Risk Assessment Completed On: 04/06/19.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are limited developmental toxicity and insufficient fertility data on nonanoic acid.

In a prenatal developmental toxicity study, 22 pregnant female Sprague Dawley rats were administered nonanoic acid via oral gavage at doses of 0 or 1500 mg/kg/day in corn oil from gestation days (GDs) 6–15. Observations included mortality, clinical signs, body weights, food and water consumption, maternal parameters (gravid uterus weight, number of corpora lutea, number of implantations, and early and late resorptions), and fetal examinations (external soft tissue, skeletal, and head examinations, body weights, and crown-rump distance). Necropsy was performed on GD 20. There were no treatment-related effects for mortality, clinical signs, body weight, food and water consumption, and necropsy. No treatment-related adverse effects were reported for pregnancy rates, corpora lutea, implantation sites, litter size, fetal viability, fetal weight, sex ratio, necropsy, or visceral and skeletal examination. Therefore, the NOAEL for maternal and developmental toxicity was considered to be 1500 mg/kg/day, the only dose tested (ECHA, 2011a,b).

Read-across material octanoic acid (CAS # 124-07-2; see Section VI) has sufficient developmental toxicity and fertility data that can be used to support the reproductive toxicity endpoint. An oral gavage OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted in Crl:CD(SD) rats. For the main study, groups of 12 males/dose were administered octanoic acid at doses of 0, 62.5, 250, or 1000 mg/kg/day in 0.5% methylcellulose, with half of these males assigned to the corresponding recovery groups. Groups of 10 females/dose were administered octanoic acid at doses of 0 or 1000 mg/kg/day, with half of these females assigned to the corresponding recovery groups. Additional groups of 5 females/dose were administered 62.5 or 250 mg/kg/day octanoic acid. Main-phase females were not used for mating. For the reproduction phase, additional groups of 12 female rats/dose (0, 62.5, 250, or 1000 mg/kg/day) were mated with males from the main study. In the main group, the animals were treated for 28 days, with a 14-day recovery period. In the reproduction group, the animals were dosed for 14 days pre-mating, and for 42–46 days during the mating and gestation periods, and up to day 4 of lactation. No treatment-related effects were noted on body weight or food consumption in males or females of the main or recovery groups. There were no treatment-related adverse effects on male and female fertility or on the development of pups up to the highest dose tested. Thus, the NOAEL for maternal and reproductive toxicity was considered to be 1000 mg/kg/day (JECDB, 2013).

The nonanoic acid MOE for the fertility endpoint can be calculated by dividing the octanoic acid NOAEL in mg/kg/day by the total systemic exposure to nonanoic acid, 1000/0.000046, or 21739130.

Data on read-across material octanoic acid did not show any developmental effects on pups up to the highest dose of 1000 mg/kg/day, which supports the single dose prenatal developmental toxicity study on the target material. Therefore, the developmental toxicity NOAEL of 1500 mg/kg/day from the prenatal developmental toxicity study was selected for the developmental toxicity endpoint. **Therefore, the nonanoic acid MOE for the developmental toxicity endpoint can be calculated by dividing the nonanoic acid NOAEL in mg/kg/day by the total systemic exposure to nonanoic acid, 1500/0.000046, or 32608696.**

In addition, the total systemic exposure to nonanoic acid (0.046 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: ECHA, 2011a.

Literature Search and Risk Assessment Completed On: 04/11/19.

11.1.4. Skin sensitization

Based on the existing data and read-across materials octanoic acid (CAS # 124-07-2) and heptanoic acid (CAS # 111-14-8), nonanoic acid does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for nonanoic acid. Based on the existing data and read-across materials octanoic acid (CAS # 124-07-2; see Section VI) and heptanoic acid (CAS # 111-14-8; see Section VI), nonanoic acid is not considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). Nonanoic acid was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens (Natsch and Haupt, 2013), and found to be positive in the U937-CD86 test (Natsch and Haupt, 2013). Read-across material octanoic acid was found to be negative in an *in vitro* DPRA and KeratinoSens (Gerberick et al., 2004a; Natsch and Gfeller, 2008, Natsch and Haupt, 2013, Natsch et al., 2013), and found to be positive in a human cell line activation test (h-CLAT) and U937-CD86 test (Nukada et al., 2011; Natsch and Haupt, 2013; Piroird et al., 2015). In a murine local lymph node assay (LLNA), nonanoic acid was found to induce a Stimulation Index (SI) of $\geq$3 when tested up to 100%, although limited details were provided (Roger et al., 2000). In 2 other LLNA reports, nonanoic acid was found to induce an SI of $\geq$3 with EC3 values of 18.77% (4692.5 μg/cm^2) and 35% (8750 μg/cm^2), respectively (Montelius et al., 1998; ECHA, 2011a; Adenuga et al., 2012). In 2 LLNAs, read-across material octanoic acid was found to be non-sensitizing up to 50% (ECHA, 2011b; Basketter et al., 1998). In a guinea pig Buehler test, nonanoic acid did not present reactions indicative of sensitization at 100% (ECHA, 2011a). In a guinea pig maximization test, read-across material heptanoic acid did not present reactions indicative of sensitization (ECHA, 2010). In a human maximization test, no skin sensitization reactions were observed with 12% (8280 μg/cm^2) nonanoic acid and 1% (690 μg/cm^2) read-across material octanoic acid (RIFM, 1976; RIFM, 1977).

Based on WoE from structural analysis, animal and human studies, and read-across materials octanoic acid and heptanoic acid, nonanoic acid does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: Ranki et al. (1983); Ayehunie et al. (2009);

Sikorski et al. (1996); Ku et al. (2008); Suzuki et al. (2009); Emter et al. (2010); Gerberick et al. (2004b); Gerberick et al. (2005); Roberts et al. (2007).

Literature Search and Risk Assessment Completed On: 04/09/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, nonanoic acid 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 nonanoic acid 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 et al., 2009). Based on the lack of absorbance, nonanoic acid 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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/03/19.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for nonanoic acid 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 nonanoic acid. Based on the Creme RIFM Model, the inhalation exposure is 0.000077 mg/day. This exposure is 18182 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: Hoffman et al. (1991); Fraser et al. (2003).

Literature Search and Risk Assessment Completed On: 04/08/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of nonanoic acid 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 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, nonanoic acid 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 nonanoic acid 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 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.

11.2.2. Risk assessment

Based on the current VoU (2015), nonanoic acid presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation

No data available.

Ecotoxicity

No data available.

Other available data

Nonanoic acid has been registered for REACH with the following additional data available at this time.

The ready biodegradability of the test material was evaluated using the CO_2 evolution test according to the OECD 301B guideline. Biodegradation of 68%–75% was observed after 28 days.

A 96-h fish (*Pimephales promelas*) acute toxicity test was conducted according to the OECD 203 method under continuous flow-through conditions. Based on the mean measured concentration, the LC50 value was reported to be 104 mg/L (95% CI: 93.4–115 mg/L).

The acute toxicity of the test material was tested on *Daphnia magna* according to EPA OPP guidelines 72-2. The 48-h EC50 was reported to be 96 mg/L (95% CL: 64–119 mg/L) (ECHA, 2011a).

11.2.3. Risk assessment refinement

Since nonanoic acid has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.52	3.52
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

The RIFM PNEC is 0.01016 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	10.16			1000000	0.01016	

Literature Search and Risk Assessment Completed On: 04/04/19.

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
- **TOXNET:** 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111683.

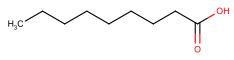
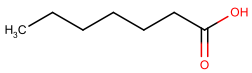
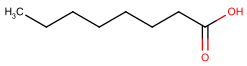
Appendix

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 material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, 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	Nonanoic acid	Heptanoic acid	Octanoic acid
CAS No.	112-05-0	111-14-8	124-07-2
Structure			
Similarity (Tanimoto Score)		0.97	1.00
Read-across Endpoint		• Skin Sensitization	• Reproductive Toxicity • Skin Sensitization
Molecular Formula	$C_9H_{18}O_2$	$C_7H_{14}O_2$	$C_8H_{16}O_2$
Molecular Weight	158.24	130.18	144.21
Melting Point (°C, EPI Suite)	12.3	−7.5	16.3
Boiling Point (°C, EPI Suite)	254.5	222.2	239
Vapor Pressure (Pa @ 25 °C, EPI Suite)	2.20E-001	1.43E+000	4.95E-001
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.42	2.42	3.05
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	207.8	2820	495.9
J_{max} (μg/cm^2/h, SAM)	31.281	179.040	77.731
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.64E-001	6.59E-002	9.04E-002
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)
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found	• No alert found
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 nonanoic acid (CAS # 112-05-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, heptanoic acid (CAS # 111-14-8) and octanoic acid (CAS # 124-07-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- The target material and the read-across analog are structurally similar and belong to a class of straight-chain aliphatic acids.
- The target material and the read-across analog share a straight aliphatic chain with an acid group.
- The key difference between the target material and the read-across analog is that the target material is a C9 straight-chain acid whereas the read-across is a C7 straight-chain acid. This structural difference is toxicologically insignificant.
- Similarity between the target material 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 material 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 material and the read-across analog.
- The target material 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.
- Octanoic acid (CAS # 124-07-2) was used as a read-across analog for the target material nonanoic acid (CAS # 112-05-0) for the skin sensitization and reproductive toxicity endpoints.
- The target material and the read-across analog are structurally similar and belong to a class of straight-chain aliphatic acids.
- The target material and the read-across analog share a straight aliphatic chain with a carboxylic acid functionality.
- The key difference between the target material and the read-across analog is that the target material is a C9 straight-chain acid whereas the read-across is a C8 straight-chain acid. This structural difference is toxicologically insignificant.
- Similarity between the target material 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 material 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 material and the read-across analog.
- The target material 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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