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Short review

RIFM fragrance ingredient safety assessment, octanoic acid, CAS Registry Number 124-07-2

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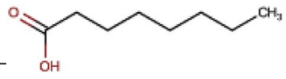

Name: Octanoic acid
CAS Registry Number: 124-07-2

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; Safford et al., 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

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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
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 et al., 2015), which should be referred to for clarifications.

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

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

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

Octanoic acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on octanoic acid and data from read-across analog nonanoic acid (CAS # 112-05-0) show that octanoic acid is not expected to be genotoxic. Data on octanoic acid provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for octanoic acid for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; octanoic acid is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to octanoic acid is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; octanoic acid was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(Heck et al., 1989; RIFM, 2014; ECHA REACH Dossier: Nonanoic Acid; ECHA, 2011a)
Repeated Dose Toxicity: NOAEL = 333.33 mg/kg/day.	JECDB (2013)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	JECDB (2013)
Skin Sensitization: Not a concern for skin sensitization under the current, declared use levels.	(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:

Critical Measured Value: 105% after 30 days (OECD 301D) (ECHA REACH Dossier: Octanoic Acid; ECHA, 2011b)

Bioaccumulation:

Screening-level: 3.16 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 24.71 mg/L (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

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Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 24.71 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.02471 μg/L

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

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1. Identification

1. **Chemical Name:** Octanoic acid
2. **CAS Registry Number:** 124-07-2
3. **Synonyms:** C-8 acid; Caprylic acid; Octylic acid; Octoic acid; Oxtylic acid; *n*-Octanoic acid; 1-Heptanecarboxylic acid; アルカン酸 (C = 4–30); Octanoic acid
4. **Molecular Formula:** $C_8H_{16}O_2$
5. **Molecular Weight:** 144.21
6. **RIFM Number:** 951
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 245.06 °C (EPI Suite)
2. **Flash Point:** 136 °C (GHS), > 200 °F; CC (FMA)
3. **Log K_{OW}:** 3.05 (Patel et al., 2002), 3.03 (EPI Suite)
4. **Melting Point**: 48.39 °C (EPI Suite)
5. **Water Solubility:** 495.9 mg/L (EPI Suite)
6. **Specific Gravity:** 0.9092 (EOA, 1976 Sample 76–37)
7. **Vapor Pressure:** 0.01 mm Hg 20 °C (FMA), 0.0313 mm Hg @ 20 °C (EPI Suite v4.0), 0.0488 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless, oily liquid with unpleasant odor and burning rancid taste; Colorless liquid solidifying in the cold to a crystalline mass or leafy crystals melting at 17 °C. Oily, rancid, sweat-like odor, repulsive to most people (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:** 0.00060% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.000019 mg/kg/day or 0.0015 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.00016 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; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** Nonanoic acid (CAS # 112-05-0)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

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

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

Blue Cheeses	Hop (*Humulus lupulus*)
Calamus (Sweet Flag) (*Acorus calamus* L.)	Licorice (*Glycyrrhiza* species)
Cheddar Cheese	Vanilla
Cheese, various types	Whiskey
Grape Brandy	Wine

*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, 2011b).

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, octanoic acid does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of octanoic acid has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537,

and TA1538 were treated with octanoic acid at concentrations up to 50000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Heck et al., 1989). Under the conditions of the study, octanoic acid was not mutagenic in the Ames test.

Further weight of evidence was made to the structurally similar analog nonanoic acid (CAS # 112-05-0; see Section VI). 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, and this can be extended to octanoic acid.

There are no data assessing the clastogenic activity of octanoic acid; however, read-across can be made to nonanoic acid (CAS # 112-05-0; see Section VI). 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 was observed at the highest 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, and this can be extended to octanoic acid.

Based on the available data, octanoic acid and read-across nonanoic acid do not present a concern for genotoxic potential.

Additional References: FDA, 1976; Zeiger et al., 1988.

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

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on octanoic acid. In an OECD 422 and GLP-compliant toxicity study, groups of 12 Sprague Dawley rats/sex/dose were administered the test material at doses of 0 (vehicle: 0.5% methylcellulose), 62.5, 250, and 1000 mg/kg through oral gavage. All animals in the main study received the treatment material for a total of 28 days (2 weeks before mating and 2 weeks after mating). Six animals/sex were treated as recovery groups and maintained for 14 days after the end of the 28-day treatment. In females of the mating group, the treatment period was a total of 42–46 days (14 days before mating, during mating and gestation, and up to day 4 of suckling. No treatment-related mortality or clinical signs were reported during the study. In addition, no treatment-related histopathological effects, with the exception of forestomach hyperplasia, were reported. Since the effects on the forestomach have no relevance to human health, these effects were not considered to be treatment-related adverse effects. Based on the absence of adverse effects at any dose level, the NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day (JECDB, 2013).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day or OECD 422/421/407 studies. 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 333.33 mg/kg/day.

Therefore, the MOE is equal to the octanoic acid NOAEL in mg/kg/day divided by the total systemic exposure to octanoic acid, 333.33/0.00016 or 2083313.

In addition, the total systemic exposure to octanoic acid (0.16 μg/kg/day) is below the TTC (30 μg/kg/day) 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 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/10/19.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on octanoic acid. 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 of 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). **Therefore, the octanoic acid MOE for the reproductive toxicity endpoint can be calculated by dividing the octanoic acid NOAEL in mg/kg/day by the total systemic exposure to octanoic acid, 1000/0.00016 or 6250000.**

In addition, the total systemic exposure to octanoic acid (0.16 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: Narotsky et al., 1994; Umweltbundesamt GmbH, 2012

Literature Search and Risk Assessment Completed On: 04/10/19.

11.1.4. Skin sensitization

Based on the existing data, octanoic acid does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, octanoic acid is not considered a skin sensitizer. The chemical structure of this material

indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). Octanoic acid was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens (Gerberick et al., 2004a; Natsch et al., 2013; Natsch and Gfeller, 2008; Natsch and Haupt, 2013). It was found to be positive in the human cell line activation test (h-CLAT) and U937-CD86 test (Nukada et al., 2011; Natsch et al., 2013; Piroird et al., 2015). In a murine local lymph node assays (LLNA), octanoic acid was found to be non-sensitizing up to 50% (ECHA, 2011b; Basketter et al., 1998). In a human maximization test, no skin sensitization reactions were observed at 1% (690 μg/cm^2) (RIFM, 1977).

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

Additional References: Suzuki et al., 2009; Emter et al., 2010; Basketter et al., 2002; Basketter et al., 2003; Gerberick et al., 2004b; Roberts et al., 2007.

Literature Search and Risk Assessment Completed On: 04/05/19.

11.1.5. Phototoxicity/Photoallergenicity

Based on the available UV/Vis spectra, octanoic 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 octanoic 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, octanoic acid does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. Key studies. There are no studies available on octanoic acid in experimental models.

11.1.5.3. 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 octanoic 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 octanoic acid. Based on the Creme RIFM Model, the inhalation exposure is 0.0015 mg/day. This exposure is 933.3 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: Smyth et al., 1962; Silver (1992); 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 octanoic 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, octanoic 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 octanoic 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 ≥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 Volume of Use (2015), octanoic acid presents no 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

Octanoic acid has been registered for REACH with the following additional data at this time:

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 105% and > 72% was observed after 30 days for 2 mg/L and 5 mg/L test concentrations, respectively.

A 96-h acute fish (Bluegill sunfish) toxicity test was conducted under static conditions. The 96-h LC50 value was reported to be 22 mg/L (95% CI: 17–31 mg/L).

A *Daphnia magna* acute immobilization test was conducted according to the OECD TG 202 method under static conditions. Based on the geometric mean measured concentration, the 48-h EC50 value was reported to be > 21 mg/L.

A *Daphnia magna* reproduction test was conducted according to the OECD 211 method under semi-static conditions. The 21-day NOEC

value was reported to be 0.2 mg/L.

A *Daphnia magna* reproduction test was conducted according to the OECD 211 method under semi-static conditions. The 21-day NOEL value was reported to be 1.294 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 based growth rate was reported to be 43.73 mg/L (95% CI: 38.40–50.37 mg/L) (ECHA, 2011b).

11.2.5. Risk assessment refinement

Since octanoic 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>24.71</u>			1000000	0.02471	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.03	3.03
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 0.02471 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

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

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
- **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. 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.2020.111271.

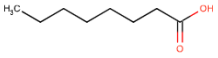
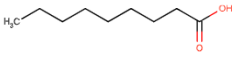
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015) and is consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment or IATA (OECD, 2015) and the European Chemicals Agency (ECHA) read-across assessment framework or RAAF (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
Principal Name	Octanoic acid	Nonanoic acid
CAS No.	124-07-2	112-05-0
Structure		
Similarity (Tanimoto Score)		1.00
Read-across Endpoint		• Genotoxicity
Molecular Formula	$C_8H_{16}O_2$	$C_9H_{18}O_2$
Molecular Weight	144.21	158.24
Melting Point (°C, EPI Suite)	16.3	12.3
Boiling Point (°C, EPI Suite)	239	254.5
Vapor Pressure (Pa @ 25 °C, EPI Suite)	4.95E-001	2.20E-001
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.05	3.42
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	495.9	207.8
J_{max} (μg/cm^2/h, SAM)	77.731	31.281
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.04E-002	1.64E-001
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Carcinogenicity (ISS)	• No alert found	• No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on octanoic acid (CAS # 124-07-2). 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, nonanoic acid (CAS # 112-05-0) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Nonanoic acid (CAS # 112-05-0) was used as a read-across analog for the target material octanoic acid (CAS # 124-07-2) for the genotoxicity endpoint.
  - •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 group.
  - •The key difference between the target material and the read-across analog is that the target material is a C8 straight-chain acid whereas the read-across is a C9 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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