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Short review

RIFM fragrance ingredient safety assessment, hexanoic acid, CAS Registry Number 142-62-1

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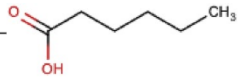

Name: Hexanoic acid
CAS Registry Number: 142-62-1

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
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

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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.
Hexanoic acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog nonanoic acid (CAS # 112-05-0) show that hexanoic acid is not expected to be genotoxic. The repeated dose and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to hexanoic acid is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data on read-across analog heptanoic acid (CAS # 111-14-8) provide a calculated MOE > 100 for the reproductive toxicity endpoint and show that there are no safety concerns for hexanoic acid for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; hexanoic acid is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; hexanoic 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, 2011)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: NOAEL = 1000 mg/kg/day. (ECHA REACH Dossier: Heptanoic Acid; ECHA, 2010)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use. (ECHA REACH Dossier: Heptanoic Acid; ECHA, 2010)
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: 84% (ISO 10708) (ECHA REACH Dossier: Heptanoic acid; ECHA, 2010)
Bioaccumulation: Screening-level: 3.16 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 141.8 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: 141.8 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.1418 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Hexanoic acid
2. **CAS Registry Number:** 142-62-1
3. **Synonyms:** Butylacetic acid; Caproic acid; Capronic acid; Hexoic acid; Pentanecarboxylic acid; Pentylformic acid; 1-Pentanecarboxylic acid; Hexylic acid; アルカン酸(C = 4–30); Hexanoic acid
4. **Molecular Formula:** $C_6H_{12}O_2$
5. **Molecular Weight:** 116.16
6. **RIFM Number:** 1104
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 202 °C (FMA), 207.76 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA)
3. **Log K_{OW}:** 1.92 (Patel et al., 2002), 2.05 (EPI Suite)
4. **Melting Point**: 26.23 °C (EPI Suite)
5. **Water Solubility:** 5898 mg/L (EPI Suite)
6. **Specific Gravity:** 0.925 (FMA), 0.9251 (EOA, 1976 Sample 76–36)
7. **Vapor Pressure:** 0.187 mm Hg @ 20 °C (EPI Suite v4.0), 0.03 mm Hg 20 °C (FMA), 0.278 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. Heavy, acrid-acid, fatty-rancid odor, often described as “sweat-like” (Arctander, Volume I, 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 v2.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0024% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000048 mg/kg/day or 0.0041 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00059 mg/kg/day (RIFM, 2019)

*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
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2. Analogs Selected:
   a. **Genotoxicity:** Nonanoic acid (CAS # 112-05-0)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** Heptanoic acid (CAS # 111-14-8)
   d. **Skin Sensitization:** 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 are available for inclusion in this safety assessment.

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

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

Blue Cheeses.
Calamus (Sweet Flag) (*Acorus calamus* L.)
Cheddar Cheese.
Cheese, Various types.
Chinese Liquor (Baijiu).
Hop (Humulus lupulus).
Licorice (*Glycyrrhiza* species).
Maize (*Zea mays* L.)
Pepper (*Piper nigrum* L.)
Swiss Cheeses.

*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, 2010).

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, hexanoic acid does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of hexanoic acid has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with hexanoic acid at concentrations up to 75,000 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, hexanoic acid was not mutagenic in the Ames test.

In addition, weight of evidence was made to nonanoic acid (CAS # 112-05-0). 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, 2011). Under the conditions of the study, nonanoic acid was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of hexanoic 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 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, hexanoic acid and read-across material nonanoic acid do not present a concern for genotoxic potential.

Additional References: Fujita and Sasaki, 1987; RIFM, 1982.

Literature Search and Risk Assessment Completed On: 04/16/19.

11.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on hexanoic acid or any read-across materials. The total systemic exposure to hexanoic acid is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on hexanoic acid or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to hexanoic acid (0.59 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.

Additional References: None.

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

11.1.3. Reproductive toxicity

The MOE for hexanoic acid 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 hexanoic acid. Read-across material heptanoic acid (CAS # 111-14-8; see Section VI) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint.

An OECD 414/GLP prenatal developmental toxicity study was conducted in inseminated female New Zealand white rabbits. Groups of 24 rabbits/dose were administered heptanoic acid via oral gavage at doses of 0, 100, 300, or 1000 mg/kg/day in carboxymethyl cellulose from day 6–28 post-coitus. Two pregnant high-dose group females were reported dead. Loud and abdominal breathing were observed for 2 or 6 days before death. One of these dead females exhibited decreased body weight and did not consume much food from the first day of treatment and had brownish nodules in the right lung at necropsy. These clinical signs and mortality were attributed to the treatment. Statistically significant reduction in food consumption was reported in the mid- and high-dose groups. No treatment-related effects were reported on gravid uterus weight or bodyweight change. No treatment-related effects were reported on fetal body weight and sex ratio. There were no treatment-related adverse effects observed for external variations or malformations and soft tissue or skeletal malformations in the litter. Thus, the NOAEL for maternal toxicity was considered to be 300 mg/kg/day, based on mortality observed among the high-dose group dams. The NOAEL for embryo-fetal development was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2010).

Additional developmental toxicity studies were conducted in rats (see table below for details), which also concluded a NOAEL of 1000 mg/kg/day for the developmental toxicity endpoint. **Therefore, the hexanoic acid MOE for the developmental toxicity endpoint can be calculated by dividing the heptanoic acid NOAEL in mg/kg/day by the total systemic exposure to hexanoic acid, 1000/0.00059 or 1694915.**

Duration in detail	GLP/Guideline	No. of animals/dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
7 days of premating, 7 days (-maximum) mating, 22 days of gestation, and up to lactation day 4	Similar to OECD 421 (deviation: female only)	10 female Sprague Dawley rats/dose (males were not treated)	Oral gavage (corn oil)	0, 200, 1000, or 2000 mg/kg/day	Fertility NOAEL = 2000 mg/kg/day Developmental toxicity NOAEL = 1000 mg/kg/day Maternal toxicity LOAEL = 200 mg/kg/day	No treatment-related adverse effects were observed up to the highest dose tested Decreased pup body weights among the high-dose group pups on day 4 of lactation Significant increases in the incidences of rales in all treatment group dams	(RIFM, 1990; Vollmuth et al., 1990; ECHA, 2010)
Gestation days 6–15	Similar to OECD 414 (deviation: single dose)	22 pregnant female Crl:COBS rats	Oral gavage (corn oil)	0 or 1000 mg/kg/day	Developmental toxicity NOAEL = 1000 mg/kg/day	No treatment-related adverse effects were observed at 1000 mg/kg/day, the only dose tested	ECHA (2010)

An OECD 408/GLP subchronic toxicity study was conducted in Sprague Dawley rats. Groups of 10 rats/sex/dose were administered heptanoic acid via oral gavage at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil for 13 weeks. In addition to systemic toxicity, reproduction parameters were also assessed. High-dose group males exhibited decreased mean testicular sperm count (19%) and daily sperm production rate (18%) when compared with controls. However, there were no associated effects on the epididymides and testes during microscopic examination. Therefore, these reported variations in testicular sperm counts and production rates were not considered to be toxicologically significant. No treatment-related adverse effects were reported on the reproductive organ weights, estrous cycle for dams, and epidydimal sperm motility, morphology and count, or on testicular sperm headcount and daily sperm production rate for males. Thus, the NOAEL for fertility effects was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2010). **Therefore, the hexanoic acid MOE for the fertility endpoint can be calculated by dividing the heptanoic acid NOAEL in mg/kg/day by the total systemic exposure to hexanoic acid, 1000/0.00059 or 1694915.**

In addition, the total systemic exposure to hexanoic acid (0.59 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a

Cramer Class I material at the current level of use.

Additional References: None.

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

11.1.4. Skin sensitization

Based on the existing data and read-across material heptanoic acid (CAS # 111-14-8), hexanoic 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 hexanoic acid. Based on the existing data and read-across material heptanoic acid (CAS # 111-14-8; see Section VI), hexanoic 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). In a guinea pig maximization test (GPMT), read-across material heptanoic acid did not present reactions indicative of sensitization up to 100% (ECHA, 2010). In a human maximization test, no skin sensitization reactions were observed with hexanoic acid at 1% (690 μg/cm^2) (RIFM, 1979).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material heptanoic acid, hexanoic acid does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/22/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, hexanoic 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 hexanoic 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, hexanoic 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 hexanoic 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 hexanoic acid. Based on the Creme RIFM Model, the inhalation exposure is 0.0041 mg/day. This exposure is 341.5 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., 1954; Smyth et al., 1962; Silver (1992).

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 hexanoic 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, hexanoic 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 hexanoic 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 Volume of Use (2015), hexanoic 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

Hexanoic 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 BODIS test according to the ISO 10708 method. Biodegradation of 84% was observed after 28 days.

A 96-h fish (fathead minnow) acute toxicity test was conducted under static conditions. The 96-h LC50 value was reported to be 88 mg/L (ECHA, 2013).

11.2.5. Risk assessment refinement

Since hexanoic 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).

- **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/

	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>141.8</u>			1000000	0.1418	

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.05	2.05
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 0.1418 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

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

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

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.2020.111263.

Appendix

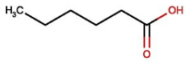
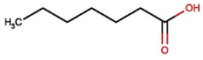
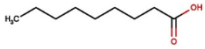
Read-across Justification

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	Hexanoic acid	Heptanoic acid	Nonanoic acid
CAS No.	142-62-1	111-14-8	112-05-0
Structure			
Similarity (Tanimoto Score)		0.89	0.86
Read-across Endpoint		• Reproductive Toxicity • Skin Sensitization	• Genotoxicity
Molecular Formula	$C_6H_{12}O_2$	$C_7H_{14}O_2$	$C_9H_{18}O_2$
Molecular Weight	116.16	130.18	158.24
Melting Point (°C, EPI Suite)	−3	−7.5	12.3
Boiling Point (°C, EPI Suite)	205.2	222.2	254.5
Vapor Pressure (Pa @ 25 °C, EPI Suite)	5.80E+000	1.43E+000	2.20E-001
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	1.92	2.42	3.42
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	1.03e+004	2820	207.8
J_{max} (μg/cm^2/h, SAM)	452.930	179.040	31.281
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.68E-002	6.59E-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
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	
Protein Binding (OECD)	• 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)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• 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 hexanoic acid (CAS # 142-62-1). 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, heptanoic acid (CAS # 111-14-8) and nonanoic acid (CAS # 112-05-0) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Heptanoic acid (CAS # 111-14-8) was used as a read-across analog for the target material hexanoic acid (CAS # 142-62-1) for the skin sensitization and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of straight-chain aliphatic acids.
  - o The target material and the read-across analog share a straight aliphatic chain with a carboxylic acid functionality.
  - o The key difference between the target material and the read-across analog is that the target material is a C6 straight-chain acid whereas the read-across is a C7 straight-chain acid. This structural difference is toxicologically insignificant.
  - o 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material 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.
- Nonanoic acid (CAS # 112-05-0) was used as a read-across analog for the target material hexanoic acid (CAS # 142-62-1) for the genotoxicity endpoint.

- o The target material and the read-across analog are structurally similar and belong to a class of straight aliphatic acids.
- o The target material and the read-across analog share a straight aliphatic chain with a carboxylic acid functionality.
- o The key difference between the target material and the read-across analog is that the target material is a C6 straight-chain acid whereas the read-across is a C9 straight-chain acid. This structural difference is toxicologically insignificant.
- o 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.
- o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o The target material 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.

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