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RIFM fragrance ingredient safety assessment, 3-methyl-5-phenylpentanenitrile, CAS Registry Number 54089-83-7

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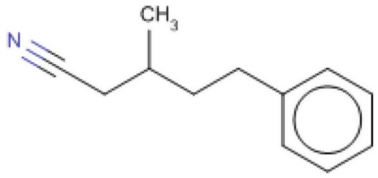

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
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, 2017) compared to a deterministic aggregate approach

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DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
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 under the limits 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 use of this material under current conditions is supported by existing information.

3-Methyl-5-phenylpentanenitrile was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data show that 3-methyl-5-phenylpentanenitrile is not genotoxic. The skin sensitization endpoint was completed using the non-reactive DST. The local respiratory toxicity endpoint was completed using the TTC for a Cramer Class III material (0.47 mg/day). The repeated dose toxicity and developmental and reproductive toxicity endpoints were completed using read-across analog 2-phenylhexanenitrile (CAS# 3508-98-3), which provided an MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2002; RIFM, 2008)
Repeated Dose Toxicity: NOAEL = 23 mg/kg/day. (ECHA, REACH: 2-phenylhexanenitrile; accessed on 11/17/2015)
Developmental and Reproductive Toxicity: NOAEL = 70 mg/kg/day. (ECHA, REACH dossier: 2-phenylhexanenitrile; accessed on 11/17/2015)
Skin Sensitization: Not a concern for skin sensitization. Exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.68 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 88.19 L/kg (EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 12.82 mg/L (RIFM Framework; Salvito, 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, 2002; #40315)
Critical Ecotoxicity Endpoint: Fish LC50: 12.82 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC: 0.01282 µg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level

1. Identification

1 **Chemical Name:** 3-Methyl-5-phenylpentanenitrile
2 **CAS Registry Number:** 54089-83-7
3 **Synonyms:** Benzenepentanenitrile, β-methyl-; Hydrocitronitrile; 3-Methyl-5-phenylpentanenitrile
4 **Molecular Formula:** $C_{12}H_{15}N$
5 **Molecular Weight:** 173.59
6 **RIFM Number:** 5734

2. Physical data

1 **Boiling Point:** 287.49 °C (EPI Suite)
2 **Flash Point:** > 93 °C (GHS)
3 **Log K_{OW}:** 3.45 (EPI Suite)
4 **Melting Point**: 41.23 °C (EPI Suite)
5 **Water Solubility:** 36.25 mg/L (EPI Suite)
6 **Specific Gravity:** Not Available
7 **Vapor Pressure:** 0.00148 mm Hg @ 20 °C (EPI Suite v4.0), 0.0027 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:** A colorless to pale yellow clear liquid with a medium floral, muguet, lily, sweet, metallic odor.*

*http://www.thegoodscentscompany.com/data/rw1112911.html#toorgano, retrieved 11/7/2015

3. Exposure

1 **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2011)
2 **95th Percentile Concentration in Body Lotion (No reported use in hydroalcoholics):** 0.017% (RIFM, 2015)
3 **Inhalation Exposure*:** 0.0012 mg/kg/day or 0.092 mg/day (RIFM, 2015)
4 **Total Systemic Exposure**:** 0.0018 mg/kg/day (RIFM, 2015)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey, 2015, 2017; Safford, 2015, 2017).

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1 **Cramer Classification:** Class III, High

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

2 Analogs Selected:
a **Genotoxicity:** None
b **Repeated Dose Toxicity:** 2-Phenylhexanenitrile (CAS # 3508-98-3)
c **Developmental and Reproductive Toxicity:** 2-Phenylhexanenitrile (CAS # 3508-98-3)
d **Skin Sensitization:** None
e **Phototoxicity/Photoallergenicity:** None
f **Local Respiratory Toxicity:** None
g **Environmental Toxicity:** None
3 Read-across Justification: See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

3-Methyl-5-phenylpentanenitrile is not reported to occur in foods by the VCF*.

*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.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; No dossier available as of 05/02/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 3-methyl-5-phe-

nylpentanenitrile does not present a concern for genetic toxicity.

10.1..1.1. Risk assessment. The mutagenic activity of 3-methyl-5-phenylpentanenitrile has been assessed in several GLP compliant Ames studies conducted in accordance with OECD TG 471. In one study, the test material induced a weak but dose-related, reproducible, and statistically significant increase in *Salmonella* strain TA1535. The test material was negative for mutagenicity in strain TA100, although both strains contain the same base pair substitution mutation (his G46). It was concluded that the material was weakly mutagenic (RIFM, 1997). To further assess the mutagenicity of the test material in a eukaryotic system, an *in vitro* mammalian gene mutation assay was conducted in mouse lymphoma cells. No toxicologically significant increases in mutant frequency at any dose level were found (RIFM, 1998). It should be noted that the purity of the material tested was not disclosed. In an additional Ames study, *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with 3-methyl-5-phenylpentanenitrile (99% pure) in dimethyl sulfoxide (DMSO) at concentrations ranging from 1.5 to 5000 μg/plate in the presence and absence of metabolic activation. 3-Methyl-5-phenylpentanenitrile did not induce a significant increase in the mutation frequency of the tester strains in the presence or absence of a metabolic activation system (RIFM, 2002). Under the conditions of the test, 3-methyl-5-phenylpentanenitrile was considered not mutagenic in the bacterial reverse mutation assay.

The clastogenic activity of 3-methyl-5-phenylpentanenitrile has been demonstrated *in vitro* by its ability to induce chromosome aberrations. 3-Methyl-5-phenylpentanenitrile was assessed for its ability to induce micronuclei in an *in vivo* mouse micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. Male and female NMRI mice were administered 3-methyl-5-phenylpentanenitrile in corn oil via oral gavage at doses of 375, 750, and 1500 mg/kg body weight. No dose-related increase in the number of micronucleated polychromatic erythrocytes was detected in the treated groups when compared to vehicle controls (RIFM, 2008). Under the conditions of the study, 3-methyl-5-phenylpentanenitrile was considered not clastogenic in mice.

Based on the available data, 3-methyl-5-phenylpentanenitrile does not present a concern for genotoxic potential.

Additional References: RIFM, 1997; RIFM, 1998; RIFM, 2007; RIFM, 2009; RIFM, 2013.

Literature Search and Risk Assessment Completed On: 09/14/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for 3-methyl-5-phenylpentanenitrile is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 3-methyl-5-phenylpentanenitrile. The isomer and read-across material 2-phenylhexanenitrile (CAS # 3508-98-3; see section V) was fed to male and female rats at actual food intake values of 134, 284, and 770 ppm equivalent to 13 and 16, 28 and 32, and 70 and 124 mg/kg bw/day for males and females, respectively, in an OECD 421/GLP reproductive and developmental toxicity screening study. The NOAEL for male and female systemic toxicity was determined to be 70 mg/kg/day for male and female rats, the highest dose tested. The male rats were treated up to 38 days, and female rats were treated up to 43–56 days. There was an increase in the relative liver weight of males and females of the highest dose group; however, this effect was considered to be adaptive in nature and not an adverse toxic effect. No other adverse effects were reported among rats fed 2-phenylhexanenitrile (ECHA, REACH dossier: 2-phenylhexanenitrile, accessed on 11/17/2015). In another 28-day OECD 407 gavage study conducted on 2-phenylhexanenitrile, 5 Sprague Dawley rats/sex/group were gavaged with 2-phenylhexanenitrile at doses of 0 (corn oil), 1, 15, and 250 mg/kg/day. Two male rats were euthanized for humane reasons from the highest dose group. The cause of mortality was primarily gastric ulcerations seen both macroscopically and microscopically. Also present were macroscopic duodenal ulcerations and microscopic mucosal ulcerations in the duodenum (RIFM, 1996). These were considered adverse effects due to treatment with 2-phenylhexanenitrile. Higher relative liver weights and lower relative prostate weights, compared to controls, were recorded among animals of the highest treatment group, with enlarged liver and swollen and necrotic hepatocytes in either sex animals and reduced colloid in prostate among male rats (seen microscopically). Such effects were not reported among any animals treated with 1 or 15 mg/kg/day. Therefore, in this particular study, the NOAEL was determined to be 15 mg/kg/day. Because the results of both of these 28-day studies demonstrate no adverse effects at a dose up to 70 mg/kg/day, the NOAEL for the repeat dose endpoint is considered 70 mg/kg/day.

A default safety factor of 3 was used when deriving a NOAEL from the 28-day OECD 407 study. The safety factor has been approved by RIFM's Independent Expert Panel*.

Thus, the derived NOAEL for the repeated dose toxicity data is 70/3 or 23 mg/kg/day.

Therefore, the 3-methyl-5-phenylpentanenitrile MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-phenylhexanenitrile NOAEL by the total systemic exposure to 3-methyl-5-phenylpentanenitrile, 23/0.0014 or 16429.

Additional References: Galibin, 1967; ECHA, REACH dossier: 2-phenylhexanenitrile (accessed on 11/17/2015).

Literature Search and Risk Assessment Completed On: 12/12/14.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 3-methyl-5-phenylpentane is adequate for the developmental and reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on 2-phenylhexanenitrile. In a dietary OECD 421/GLP developmental and reproductive toxicity screening conducted on Wistar Han rats, groups were administered 2-phenylhexanenitrile via gavage at nominal values of 0, 200, 400, and 1000 ppm (equivalent to doses of 0, 15, 30, and 70–73 mg/kg bw/day for the males and 79–124 mg/kg bw/day for the females). There were no adverse developmental effects observed among the pups of female animals fed the diet containing the test material up to the highest dose levels of 79–124 mg/kg/day. Thus, the NOAEL for developmental toxicity was determined to be 80 mg/kg/day (ECHA, REACH dossier: 2-phenylhexanenitrile, accessed on 11/17/2015). There was no adverse effect of test material administration towards the male and female reproductive organs up to the highest dose tested. Thus, the NOAEL for male and female reproductive toxicity was determined to be 70 mg/kg/day, the highest dose tested in male rats (ECHA, REACH dossier: 2-phenylhexanenitrile, accessed on 11/17/2015).

Therefore, the 3-methyl-5-phenylpentanenitrile MOE for the developmental and reproductive toxicity endpoint can be calculated by dividing the 2-phenylhexanenitrile NOAEL by the total systemic exposure to 3-methyl-5-phenylpentanenitrile, 70/0.0014 or 50,000.

Additional References: Galibin, 1967.

Literature Search and Risk Assessment Completed On: 12/12/14.

10.1.4. Skin sensitization

Based on the existing data and application of DST, 3-methyl-5-phenylpentanenitrile does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. The chemical structure of this material

Table 1
Acceptable exposure limits for 3-methyl-5-phenylpentanenitrile based on non-reactive DST.

IFRA Category[a]	Examples of Product Type	Calculated QRA
1	Lip Products	0.026%
2	Deodorant/Antiperspirant	0.033%
3	Hydroalc., Shaved Skin	0.136%
4	Hydroalc., Unshaved Skin	0.407%
5	Women Facial Cream	0.214%
6	Mouthwash	0.652%
7	Intimate Wipes	0.068%
8	Hair Styling Aids Non-Spray	0.91%
9	Conditioners, Rinse-off	4.50%
10	Hard Surface Cleaners	2.5%
11	Candle (Non-Skin/Incidental Skin)	Not Restricted

Note.
[a] For a description of the categories, refer to the QRA Informational Booklet. (www.rifm.org/doc/QRAInfoJuly2011.pdf).

indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree 2.6.6; OECD toolbox v3.3). In an alternative local lymph node assay, no differences were observed in ear thickness, ear weight, lymph node weight, and lymph node cell count in animals treated with 100% 3-methyl-5-phenylpentanenitrile when compared with vehicle-treated controls (RIFM, 2005). Moreover, no reactions were observed with 10% 3-methyl-5-phenylpentanenitrile in guinea pigs and humans (Haarmann & RIFM, 1980). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2. The current 95th percentile dermal exposure is below the DST for non-reactive materials when evaluated in all QRA categories. 3-Methyl-5-phenylpentanenitrile does not present a concern for skin sensitization (see Table 1).

Based on weight of evidence from structural analysis, and animal and human study reports, 3-methyl-5-phenylpentanenitrile does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/28/16.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 3-methyl-5-phenylpentanenitrile would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 3-methyl-5-phenylpentanenitrile in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on lack of absorbance, 3-methyl-5-phenylpentanenitrile does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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, 1000 L mol^{-1} · cm^{-1}, for phototoxic effects (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/07/16.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level of 3-methyl-5-phenylpentanenitrile is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 3-methyl-5-phenylpentanenitrile. Based on the Creme RIFM model, the inhalation exposure is 0.092 mg/day. This exposure is 5.1 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 9/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3-methyl-5-phenylpentanenitrile was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3-methyl-5-phenylpentanenitrile 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 v4.1 did not identify 3-methyl-5-phenylpentanenitrile as either being possibly persistent nor bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental

fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), 3-methyl-5-phenylpentanenitrile does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.2.1. Other available data. 3-Methyl-5-phenylpentanenitrile has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

	LC50 (Fish) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	12.82			1,000,000	0.01282	

Endpoints used to calculate PNEC are underlined. Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.45	3.45
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1t
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.01282 µg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 12/2/14.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2018.09.072.

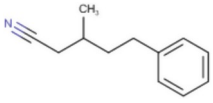
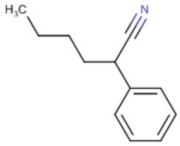
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity 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 Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite (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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target material	Read-across material
Principal Name	3-Methyl-5-phenylpentanenitrile	2-Phenylhexanenitrile
CAS No.	54089-83-7	3508-98-3
Structure		
Similarity (Tanimoto score)[1]		0.794
Read-across endpoint		• Developmental & Reproductive • Repeated dose
Molecular Formula	$C_{12}H_{15}N$	$C_{12}H_{15}N$
Molecular Weight	173.59	172.12
Melting Point (°C, EPI Suite)	41.23	41.23
Boiling Point (°C, EPI Suite)	287.49	265–276.5
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.359	6.4
Log Kow (KOWWIN v1.68 in EPI Suite)	3.45	3.14
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	36.25	37.7
J_{max} (mg/cm^2/h, SAM)	18.548	15.402
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.66E-006	7.66E-006
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, without OH and NH_2 group	• Non-binder, without OH and NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (low reliability)	• Toxicant (low reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 3-methyl-5-phenylpentanenitrile (CAS # 54089-83-7). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 2-phenylhexanenitrile (CAS # 3508-98-3) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- 2-Phenylhexanenitrile (CAS # 3508-98-3) is used as a structurally similar read-across analog for the target material 3-methyl-5-phenylpentanenitrile (CAS # 54089-83-7) for the repeated dose, reproductive, and developmental toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of aliphatic nitriles with an aryl moiety.
  - o The target substance and the read-across analog have the aliphatic nitrile insulated from the aryl moiety common among them.
  - o The key difference between the target substance and the read-across analog is that the target has a longer aliphatic chain between the nitrile group and aryl moiety compared to the read-across material. This structural difference between the target substance and the read-across analog do not raise additional structural alerts, so the structure differences are toxicologically insignificant.
  - o The target substance and the read-across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the aliphatic nitrile and aromatic ring. The differences in the structure responsible for Tanimoto score < 1 are toxicologically insignificant.
  - o The target substance and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties

of the target substance and the read-across analog are estimated to be toxicologically insignificant for repeated dose, reproductive, and developmental toxicity endpoints.

- o According to the QSAR OECD Toolbox (v3.4), structural alerts for repeated dose, reproductive, and developmental toxicity endpoints are consistent between the target substance and the read-across analog. The read-across analog is predicted to be a toxicant for the developmental endpoint with low reliability only by CAESAR model v.2.1.6. The data described in the developmental and reproductive section supports that the read-across material is safe to use within the given margin of exposure and level of use for the developmental toxicity endpoint, so these *in silico* predictions will be superseded.
- o The target substance and the read-across analog are expected to be metabolized similarly as shown by metabolism simulator.
- o The structural alerts for the repeated dose, reproductive, and developmental toxicity endpoints are consistent between the metabolites of the read-across analog and the target substance.
- o The structural differences between the target substance and the read-across analog are deemed to be toxicologically insignificant.

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