Food and Chemical Toxicology 176 (2023) 113819

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, 2-phenylhexanenitrile, CAS registry number 3508-98-3

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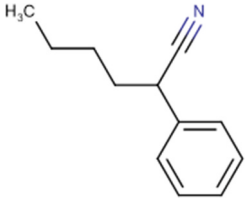
ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

Version: 032823. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: 2-PhenylhexanenitrileCAS



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Registry Number: 3508-98-3

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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch

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https://doi.org/10.1016/j.fct.2023.113819
Received 29 March 2023; Received in revised form 1 May 2023; Accepted 8 May 2023
Available online 16 May 2023

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test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

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

DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

DRF - Dose Range Finding

DST - Dermal Sensitization Threshold

EC_{50} - Effective Concentration 50%

ECHA - European Chemicals Agency

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

EU - Europe/European Union

GLP - Good Laboratory Practice

IFRA - The International Fragrance Association

LC_{50} - Lethal Concentration 50%

LOEL - Lowest Observed 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.

2-Phenylhexanenitrile was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-phenylhexanenitrile is not genotoxic. Data on 2-phenylhexanenitrile provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across material 2-methyldecanenitrile (CAS # 69300-15-8) show that there are no safety concerns for 2-phenylhexanenitrile for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-phenylhexanenitrile is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 2-phenylhexanenitrile is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 2-phenylhexanenitrile was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1996a; RIFM, 1996b)
Repeated Dose Toxicity: NOAEL = 23 mg/kg/day.	ECHA (2013)
Reproductive Toxicity: NOAEL = 70 mg/kg/day.	ECHA (2013)
Skin Sensitization: Not a sensitization concern.	RIFM (2009)
Photoirritation/Photoallergenicity: Not expected to be a photoirritant/photoallergen.	(UV/Vis spectra; RIFM Database)
Local Respiratory Toxicity: NO NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

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Hazard Assessment:	
Persistence:	
Critical Measured Value: 0% (OECD 301D)	RIFM (1996h)
Bioaccumulation:	
Screening-level: 88.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-h Algae EC_{50}: 0.509 mg/L	(EPI Suite v4.11; US EPA, 2012a)
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: 96-h Algae EC_{50}: 0.509 mg/L	(EPI Suite v4.11; US EPA, 2012a)
RIFM PNEC is: 0.0509 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: <1	

1. Identification

1. **Chemical Name:** 2-Phenylhexanenitrile
2. **CAS Registry Number:** 3508-98-3
3. **Synonyms:** Salicynalva; Hexanenitrile, 2-phenyl-; 2-Phenylhexanenitrile
4. **Molecular Formula:** $C_{12}H_{15}N$
5. **Molecular Weight:** 173.25 g/mol
6. **RIFM Number:** 6474
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 265 °C–276.5 °C at 1012 mbar (RIFM, 1996i)
2. **Flash Point:** 128.5 °C (Globally Harmonized System), 128.5 °C (RIFM, 1996i)
3. **Log K_{OW}:** 3.14 (RIFM, 1996i)
4. **Melting Point**: 41.23 °C (EPI Suite v4.11)
5. **Water Solubility:** 3.63E+01 (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00148 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2019)

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

1. **95**th **Percentile Concentration in Fine Fragrance::** 0.25% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00042 mg/kg/day or 0.027 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0054 mg/kg/day (RIFM, 2019)

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

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
III	III	III

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-Methyldecanenitrile (CAS # 69300-15-8); weight of evidence (WoE) material benzonitrile (CAS # 100-47-0)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

2-Phenylhexanenitrile 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.

9. REACH dossier

Available (ECHA, 2013); accessed on 06/27/22.

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, 2-phenylhexanenitrile does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenicity of 2-phenylhexanenitrile was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *Escherichia coli* WP2uvrA were treated with 2-phenylhexanenitrile in dimethyl sulfoxide

(DMSO) at doses of 39.063, 78.125, 156.25, 312.5, 625, 1250, 2500, and 5000 μg/plate in the presence and absence of metabolic activation. There were no increases in the number of revertants for any of the treatments either in the presence or absence of S9 metabolic activation (RIFM, 1996a). Under the conditions of the study, it was concluded that 2-phenylhexanenitrile is not mutagenic in bacteria.

The clastogenic potential of 2-phenylhexanenitrile was evaluated in an *in vitro* chromosome aberration assay conducted in compliance with GLP regulations in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with 2-phenylhexanenitrile in DMSO at concentrations ranging between 3.9 and 500 μg/mL in the presence and absence of S9 metabolic activation for 3 or 32 h. Following treatment, cells were harvested, washed, fixed, stained with Giemsa, and evaluated for the presence of chromosome aberrations. 2-phenylhexanenitrile did not induce binucleated cells with micronuclei in either non-activated or S9-activated test systems (RIFM, 1996b). Under the conditions of this study, 2-phenylhexanenitrile was not clastogenic in cultured human lymphocytes.

Based on the available data, 2-phenylhexanenitrile does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/14/22.

11.1.2. Repeated dose toxicity

The MOE for 2-phenylhexanenitrile is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 2-phenylhexanenitrile.

In a GLP- and OECD 421-compliant study, groups of 10 Wistar Han rats/sex/dose were administered 2-phenylhexanenitrile via diet at concentrations of 0, 200, 400, and 1000 parts per million (ppm) (equivalent to doses of 0, 15, 30, and 70 mg/kg/day) for 28 days. Based on no adverse effects observed up to the highest dose, the repeated dose toxicity NOAEL for this study was considered to be 70 mg/kg/day (ECHA, 2013).

In an OECD 407-compliant study, groups of 5 Sprague Dawley rats/sex/dose were administered 2-phenylhexanenitrile via gavage (vehicle: corn oil) at doses of 0, 1, 15, and 250 mg/kg/day for 28 days. An additional 5 Sprague Dawley rats/sex/dose at 0 and 250 mg/kg/day were maintained for 2 weeks after the treatment period as recovery groups. Two males at the high dose were euthanized on days 5 and 7 due to gastric ulcerations seen both macroscopically and microscopically in addition to the presence of macroscopic duodenal ulcerations and microscopic mucosal ulcerations in the duodenum. The pathology underlying these euthanizations was considered treatment-related and adverse. Food consumption and body weights were lower in males at the high dose, but this effect was reversed during the recovery period. Relative liver weights were reduced in males and females at the high dose, but this effect was reversed during the recovery period. Based on mortality observed at 250 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered to be 15 mg/kg/day (RIFM, 1996d).

Because the results of these two 28-day studies demonstrate no adverse effects at doses 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 OECD 407 study (ECHA, 2012). The safety factor has been approved by The Expert Panel for Fragrance Safety*.

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

Therefore, the MOE for 2-phenylhexanenitrile is equal to the 2-phenylhexanenitrile NOAEL in mg/kg/day divided by the total systemic exposure for 2-phenylhexanenitrile, 23/0.0054 or 4259.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/13/22.

11.1.3. Reproductive toxicity

The MOE for 2-phenylhexanenitrile 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 2-phenylhexanenitrile.

In a GLP- and OECD 421-compliant study, groups of 10 Wistar Han rats/sex/dose were administered 2-phenylhexanenitrile via diet at concentrations of 0, 200, 400, and 1000 ppm (equivalent to doses of 0, 15, 30, and 70 mg/kg/day) for 28 days. Based on no adverse effects observed up to the highest dose, the developmental toxicity and fertility NOAEL for this study was considered to be 70 mg/kg/day (ECHA, 2013).

Therefore, the 2-phenylhexanenitrile MOE for the reproductive toxicity endpoints can be calculated by dividing the 2-phenylhexanenitrile NOAEL by the total systemic exposure to 2-phenylhexanenitrile, 70/0.0054 or 12963.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/13/22.

11.1.4. Skin sensitization

Based on existing data on the target material, read-across material 2-methyldecanenitrile (CAS # 69300-15-8), and WoE material benzonitrile (CAS # 100-47-0), 2-phenylhexanenitrile presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for 2-phenylhexanenitrile. Therefore, read-across material 2-methyldecanenitrile (CAS # 69300-15-8; see Section VI) and WoE material benzonitrile (CAS # 100-47-0; see Section VI) were used for the risk assessment of 2-phenylhexanenitrile. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, 2-phenylhexanenitrile is not considered a skin sensitizer. The chemical structures of the read-across material and the target material indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). The read-across material, 2-methyldecanenitrile, was not predicted to be a sensitizer in a direct peptide reactivity assay (DPRA) and a KeratinoSens assay (RIFM, 2016a; RIFM, 2016b). In a human cell line activation test (h-CLAT), the read-across material was predicted to be a sensitizer (RIFM, 2016c). In an LLNA, the read-across material was not found to be sensitizing when tested up to 100% (25000 μg/cm^2) (RIFM, 2009). In a guinea pig maximization test and a guinea pig Buehler test, the read-across material did not present reactions indicative of sensitization (RIFM, 1989; RIFM, 1982). Similarly, in a guinea pig maximization test, no reactions were observed with 2-phenylhexanenitrile (RIFM, 1996c). Additionally, in a Confirmation of No Induction in Humans test (CNIH), no sensitization reactions were observed in the 56 volunteers with the target material at 2203 μg/cm^2 (RIFM, 1995). In a separate CNIH with 2500 μg/cm2 of read-across material 2-methyldecanenitrile, no reactions indicative of sensitization were observed in any of the 101 volunteers at 2250 μg/cm^2 (RIFM, 2010). A CNIH with 1417 μg/cm^2 of WoE material benzonitrile in 1:3 ethanol:diethyl phthalate (DEP) led to no reactions indicative of sensitization observed in any of the 112 volunteers (RIFM, 2017).

Based on WoE from structural analysis, *in vitro* studies, animal studies, and human studies on the read-across material and WoE material, as well as the target material, 2-phenylhexanenitrile does not

Table 1
Summary of existing data on 2-methyldecanenitrile as a read-across for 2-phenylhexanenitrile.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
No evidence of sensitization[g]	2250	N/A	N/A	N/A	Negative up to 25000 (100%)	Negative	Negative
	***In vitro* Data[f]**			***In silico* protein binding alerts(OECD Toolbox v4.5)**			
	KE 1	**KE 2**	**KE 3**	**Target Material**	**Autoxidation simulator**	**Metabolism simulator**	
	Negative	Negative	Positive	No alert found	No alert found	No alert found	

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; GPMT = Guinea Pig Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[e] Studies conducted according to the OECD TG 406 are included in the table.

[f] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[g] Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

present a concern for skin sensitization.

Additional References: RIFM, 1977.

Literature Search and Risk Assessment Completed On: 02/06/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, 2-phenylhexanenitrile would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for 2-phenylhexanenitrile in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-phenylhexanenitrile does not present a concern for photoirritation or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/28/22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-phenylhexanenitrile is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-phenylhexanenitrile. Based on the Creme RIFM Model, the inhalation exposure is 0.027 mg/day. This exposure is 17.4 times lower than the Cramer Class III TTC value of 0.47 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: None.

Literature Search and Risk Assessment Completed On: 10/12/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-phenylhexanenitrile 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 of 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 2-phenylhexanenitrile was identified as a fragrance material with the 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 2-phenylhexanenitrile as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). 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.

11.2.1.1. Risk assessment. Based on the current VoU (2019), 2-phenylhexanenitrile presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 1996h: The ready biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D method. No biodegradation was observed after 28 days.

11.2.1.2.2. Ecotoxicity. RIFM, 1996e: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. Under the conditions of the study, 48-h EC_{50} was 1.6 mg/L.

RIFM, 1996f: A 96-h fish (rainbow trout) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. Under the conditions of this study, the 96-h LC_{50} was 2.2 mg/L.

RIFM, 1996g: An algal growth inhibition test was conducted following the OECD TG 201. Under the test conditions, the test material was inhibitory to the growth of algae at concentrations greater than 0.26 mg/L.

11.2.1.2.3. Other available data. 2-Phenylhexanenitrile has been registered for REACH but has no additional data available.

11.2.1.3. Risk assessment refinement. Since 2-phenylhexanenitrile has passed the screening criteria, measured data are included for completeness only and have 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 Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.14	3.14
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	1–10	<1
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 0.0509 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 10/04/22.

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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **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 03/28/23.

	LC_{50} (Fish) (mg/L)	EC_{50} (*Daphnia*) (mg/L)	EC_{50} (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	23.66			1000000	0.02366	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.779	7.038	0.509	10000	0.0509	Benzyl Nitriles
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	7.050	4.578	5.939			Neutral Organic SAR (Baseline toxicity)

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.113819.

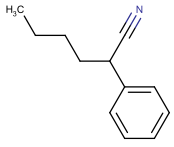
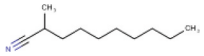
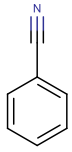
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017b).

- 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 (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 v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material	WoE Material
Principal Name	2-Phenylhexanenitrile	2-Methyldecanenitrile	Benzonitrile
CAS No.	3508-98-3	69300-15-8	100-47-0
Structure			
Similarity (Tanimoto Score)		0.28	0.33
SMILES	CCCCC(C#N)c1ccccc1	CCCCCCCCC(C)C#N	N#Cc1ccccc1
Endpoint		Skin sensitization	Skin sensitization
Molecular Formula	$C_{12}H_{15}N$	$C_{11}H_{21}N$	C_7H_5N
Molecular Weight (g/mol)	173.259	167.296	103.124
Melting Point (°C, EPI Suite)	41.23	11.56	−12.70
Boiling Point (°C, EPI Suite)	287.49	250.43	191.10
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.60E-01	3.55E+00	1.02E+02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.63E+01	8.89E+00	2.00E+03
Log K_{OW}	3.45	4.2	1.56
J_{max} (μg/cm^2/h, SAM)	3.26	1.40	70.46
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.76E-01	3.96E+01	5.28E+00
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found	No alert found	No alert found
Protein Binding (OECD)	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ α-Halobenzyls (and related cyano, sulfate, and sulphonate subs. chem.)	No alert found	No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	WoE Material
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified	No skin sensitization reactivity domain alerts were identified	No skin sensitization reactivity domain alerts were identified
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 2-phenylhexanenitrile (CAS # 3508-98-3). 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, 2-methyldecanenitrile (CAS # 69300-15-8) and benzonitrile (CAS # 100-47-0) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 2-Methyldecanenitrile (CAS # 69300-15-8) was used as a read-across analog for the target material, 2-phenylhexanenitrile (CAS # 3508-98-3), for the skin sensitization endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to the group of alkyl nitriles.
  - ○ The key difference between the target material and the read-across analog is the target material is a phenyl nitrile, whereas the read-across analog is a methyl nitrile.
  - ○ The 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 v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - ○ The target material has an alert for SN2 in the skin sensitization endpoint. There are no other alerts for the target material, and the read-across analog displays no *in silico* alerts. Based on the data from the skin sensitization section for the target material, it is determined not to be a skin sensitizer. The predictions are superseded by the data.
  - ○ 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.
- Benzonitrile (CAS # 100-47-0) was used as a WoE analog for the target material, 2-phenylhexanenitrile (CAS # 3508-98-3), for the skin sensitization endpoint.
  - ○ The target material and the WoE analog are structurally similar and belong to the group of aryl nitriles.
  - ○ The WoE analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - ○ The similarity between the target material and the WoE 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 WoE analog are sufficiently similar to enable a comparison of their toxicological properties.
  - ○ Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40% and J_{max} for the WoE analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - ○ According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the WoE analog.
  - ○ The target material has an alert for SN2 in the skin sensitization endpoint. There are no other alerts for the target material, and the WoE analog displays no *in silico* alerts. Based on the data from the skin sensitization section for the target material, it is determined not to be a skin sensitizer. The predictions are superseded by the data.
  - ○ The target material and the WoE 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 WoE analog and the target material.

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