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RIFM fragrance ingredient safety assessment, octanenitrile, CAS Registry Number 124-12-9

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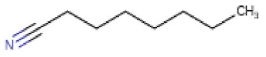

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Name: Octanenitrile CAS Registry Number: 124-12-9

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

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CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch 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., 2015a, 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
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, 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.

Octanenitrile was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog hexanenitrile (CAS # 628-73-9) show that octanenitrile is not expected to be genotoxic. Data on read-across analog dodecanenitrile (CAS # 2437-25-4) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for octanenitrile for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; octanenitrile is not expected to be phototoxic/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 octanenitrile is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; octanenitrile 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 in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2017a; RIFM, 2017b)
Repeated Dose Toxicity: NOAEL = 16.7 mg/kg/day.	(ECHA REACH Dossier: Dodecanenitrile; ECHA, 2017a)
Reproductive Toxicity: NOAEL = 250 mg/kg/day.	(ECHA REACH Dossier: Dodecanenitrile; ECHA, 2017a)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	Natsch (2013)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 3.13 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 30.3 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 33.98 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)
Critical Ecotoxicity Endpoint: Fish LC50: 33.98 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.03398 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Octanenitrile
2. **CAS Registry Number:** 124-12-9
3. **Synonyms:** 1-Cyanoheptane; Arneel 8; Heptylcyanide; n-Heptyl cyanide; n-Octanonitrile; Octanenitrile
4. **Molecular Formula:** $C_8H_{15}N$
5. **Molecular Weight:** 125.21 g/mol
6. **RIFM Number:** 6381
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 205.95 °C (EPI Suite)
2. **Flash Point:** 85 °C (Globally Harmonized System)
3. **Log K_{OW}:** 2.8 (EPI Suite)
4. **Melting Point**: 10.83 °C (EPI Suite)
5. **Water Solubility:** 233.7 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.187 mm Hg at 20 °C (EPI Suite v4.0), 0.278 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; the 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. 0.1–1 metric ton per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Cleaning Wipes:** 0.0048% (RIFM, 2019)

(No reported use in Fine Fragrance)

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0000001 mg/kg/day (RIFM, 2019)

*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 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, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
III	III	III

2. Analogs Selected:
   a. **Genotoxicity:** Hexanenitrile (CAS # 628-73-9)
   b. **Repeated Dose Toxicity:** Dodecanenitrile (CAS # 2437-25-4)
   c. **Reproductive Toxicity:** Dodecanenitrile (CAS # 2437-25-4)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

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

Pork

*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; accessed on 10/25/21.

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, octanenitrile does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Octanenitrile was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of octanenitrile; however, read-across can be made to hexanenitrile (CAS # 628-73-9; see Section VI).

The mutagenic activity of hexanenitrile 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 hexanenitrile 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 (RIFM, 2017a). Under the conditions of the study, hexanenitrile was not mutagenic in the Ames test.

The clastogenic activity of hexanenitrile 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 hexanenitrile in DMSO at concentrations up to 972 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 972 μg/mL in the presence and absence of metabolic activation. Hexanenitrile did induce binucleated cells with micronuclei at 159 μg/mL in the 24-h treatment in the absence of an S9 activation system (RIFM, 2017b). However, this increase was only observed at the lowest dose and was within the historical control range, and therefore was considered to be not biologically relevant. Under the conditions of the study, hexanenitrile was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, hexanenitrile does not present a concern for genotoxic potential, and this can be extended to octanenitrile.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.2. Repeated dose toxicity

The MOE for octanenitrile is adequate for the repeated dose toxicity

endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on octanenitrile. Read-across material dodecanenitrile (CAS # 2437-25-4; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In an OECD 422-compliant study, groups of 10 Wistar rats/sex/dose were administered dodecanenitrile via gavage (vehicle: 2% methylcellulose) at doses of 0, 50, 250, or 1000 mg/kg/day. Dodecanenitrile was administered to male rats for at least 28 days and to female rats for 14 days prior to pairing, through the pre-pairing, pairing, and gestation periods until the F1 generation reached day 4 postpartum. Mortality and alteration in clinical signs were reported among the high-dose group of females. Alterations in clinical signs were also reported among high-dose males and mid-dose females. Hematological alterations were reported among high-dose males; however, the significance remained unknown. During gross necropsy, the high-dose males were reported to have an enlarged liver and a reduction in thymus size. High-dose females were reported to have an enlarged liver, stomach with discolorations, crateriform retractions and foci, and enlarged adrenal glands. Secondary to the spontaneous deaths, the start of autolysis, ileum distended with gas, discoloration, incompletely collapsed lungs, distended urinary bladder, and discoloration of the liver were observed. High-dose males had a significant increase in absolute and relative liver weights. Histopathological examination revealed minimal to moderate centrilobular to diffuse hepatocellular hypertrophy and atrophy/involution in the thymus among high-dose group males. Mid- and high-dose males showed ulceration, erosion, and mucosal necrosis in the forestomach and glandular stomach. High-dose male kidneys showed an increase in tubular basophilia. High-dose females showed moderate, centrilobular to diffuse hepatocellular hypertrophy along with incidences of moderate centrilobular necrosis and apoptosis. Increased incidence of ulceration, erosion, and mucosal necrosis in the forestomach and glandular stomach were reported among mid- and high-dose females. Ulceration was also reported to occur in the duodenum of high-dose females. Thus, the NOAEL was considered to be 50 mg/kg/day, based on histopathological alterations in the GI tract and liver, along with clinical signs among males and females of higher dose groups and mortality among high-dose group females (ECHA, 2017a).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 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 50/3, or 16.7 mg/kg/day.

Therefore, the octanenitrile MOE for the repeated dose toxicity endpoint can be calculated by dividing the dodecanenitrile NOAEL in mg/kg/day by the total systemic exposure to octanenitrile, 16.7/0.0000001, or 167000000.

In addition, the total systemic exposure to octanenitrile (0.0001 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/22/21.

11.1.3. Reproductive toxicity

The MOE for octanenitrile 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 octanenitrile. Read-across material dodecanenitrile (CAS # 2437-25-4; see Section VI) has sufficient data to support the reproductive toxicity endpoints. In an OECD 422-compliant study, groups of 10 Wistar rats/sex/dose were administered dodecanenitrile via gavage (vehicle: 2% methylcellulose) at doses of 0, 50, 250, or 1000 mg/kg/day. Dodecanenitrile was administered to male rats for at least 28 days and to female rats for 14 days prior to mating, through the pre-mating, mating, and gestation periods until the F1 generation reached day 4 postpartum. At the high dose, 4 dams died spontaneously on day 1 postpartum, and 2 dams were euthanized in extremis on days 1 and 4 postpartum. Statistically significant decreases in birth and viability indices were observed at the high dose. At the high dose, pup body weight was slightly reduced on day 1 postpartum but distinctly reduced on day 4 postpartum; however, the results were based only on the data of one litter. Thus, the fertility NOAEL for this study was considered to be 250 mg/kg based on maternal death at the high dose. The developmental toxicity NOAEL for this study was considered to be 250 mg/kg/day based on decreased pup body weights and decreased birth and viability indices at high-dose (ECHA, 2017a).

Therefore, the octanenitrile MOE for the reproductive toxicity endpoint can be calculated by dividing the dodecanenitrile NOAEL in mg/kg/day by the total systemic exposure to octanenitrile, 250/0.0000001, or 2500000000.

In addition, the total systemic exposure to octanenitrile (0.0001 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/22/21.

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. Based on the existing data, octanenitrile is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Octanenitrile was found to be negative in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens, and U-SENS test (Natsch, 2013). In a Buehler test, octanenitrile did not present reactions indicative of sensitization (RIFM, 1989).

Based on a weight of evidence (WoE) from structural analysis and *in vitro* and animal studies, octanenitrile does not present a concern for skin sensitization.

Additional References: Patlewicz (2007).

Literature Search and Risk Assessment Completed On: 10/12/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, octanenitrile 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 octanenitrile 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 phototoxicity and photoallergenicity (Henry, 2009bib_Henry_et_al_2009bib_Henry_et_al_2009bib_Henry_et_al_2009). Based on the lack of absorbance, octanenitrile does not present a concern for phototoxicity or photoallergenicity.

11.1.6. 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 phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/28/21.

11.1.7. Local Respiratory Toxicity

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

11.1.7.1. Risk assessment. There are no inhalation data available on octanenitrile. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is 4700 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: 10/15/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of octanenitrile 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, octanenitrile 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 octanenitrile 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), octanenitrile presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. No data available.

11.2.2.2. Ecotoxicity. No data available.

11.2.2.3. Other available data. Octanenitrile has been pre-registered for REACH with no additional data at this time.

11.2.2.4. Risk assessment refinement. 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, 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.8	2.8
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<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 0.03398 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 10/05/21.

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
- **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 HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	33.98			1000000	0.03398	

links listed above were active as of 02/28/22.

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.2022.113112.

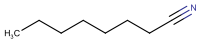
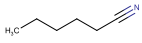
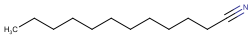
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 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 v4.2 (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Octanenitrile	Hexanenitrile	Dodecanenitrile
CAS No.	124-12-9	628-73-9	2437-25-4
Structure			
Similarity (Tanimoto Score)		0.81	1.00
SMILES	CCCCCCCC#N	CCCCCC#N	CCCCCCCCCCCC#N
Endpoint		Genotoxicity	Repeated dose toxicity Reproductive toxicity

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Molecular Formula	$C_8H_{15}N$	$C_6H_{11}N$	$C_{12}H_{23}N$
Molecular Weight (g/mol)	125.21	97.16	181.32
Melting Point (°C, EPI Suite)	−45.60	−80.30	4.00
Boiling Point (°C, EPI Suite)	205.20	163.60	277.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.20E+01	3.80E+02	3.15E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.34E+02	2.48E+03	2.51E+00
Log KOW	2.75	1.66	4.77
J_{max} (μg/cm^2/h, SAM)	23.66	116.35	0.42
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.69E+01	9.62E+00	5.26E+01
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	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Aliphatic nitriles (Hepatotoxicity) Rank B	Aliphatic nitriles (Hepatotoxicity) Rank B	Aliphatic nitriles (Hepatotoxicity) Rank B
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)	Non-toxicant (low reliability)
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 the target material octanenitrile (CAS # 124-12-9). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, dodecanenitrile (CAS # 2437-25-4) and hexanenitrile (CAS # 628-73-9) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusions

- Hexanenitrile (CAS # 628-73-9) was used as a read-across analog for the target material octanenitrile (CAS # 124-12-9) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aliphatic saturated nitriles.
  - o The target material and the read-across analog share a decanenitrile substructure.
  - o The key difference between the target material and the read-across analog is the length of the aliphatic chain, which differs by only 2 carbons. The read-across 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.
  - o 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.
  - 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 QSAR OECD Toolbox, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no *in silico* alerts for the target material or the read-across analog, which is consistent with data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural differences between the target material and the read-across analog do not affect consideration of the toxicological endpoints.
- Dodecanenitrile (CAS # 2437-25-4) was used as a read-across analog for the target material octanenitrile (CAS # 124-12-9) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aliphatic saturated nitrile.
  - o The target material and the read-across analog share a decanenitrile substructure.
  - o The key difference between the target material and the read-across analog is the length of the aliphatic chain, which differs by only 1 or 2 carbons. The read-across 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.
  - o 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.
  - 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 The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq$80% skin absorption for the target material, while it translates to $\leq$40% absorption for the read-across analog. While percentage skin absorption estimated from J_{max} values indicate exposure of the substance, they do not represent hazard or toxicity parameters. Therefore, the J_{max} of the target material and the

appropriate read-across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.

- o According to the QSAR OECD Toolbox, 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 categorized as aliphatic nitriles Rank B with a hepatotoxicity alert by HESS categorization for repeated dose toxicity. The data described in the repeated dose toxicity section show that the MOE for the read-across analog is adequate at the current level of use. Therefore, this alert will be superseded by the availability of the data.
- o There are no *in silico* alerts for the target material or the read-across analog, which is consistent with data.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural differences between the target material and the read-across analog do not affect consideration of the toxicological endpoints.

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