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Short review

RIFM fragrance ingredient safety assessment, dodecanenitrile, CAS Registry Number 2437-25-4

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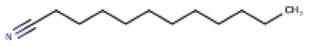

Name: Dodecanenitrile

CAS Registry Number: 2437-25-4

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; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach

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

DST - Dermal Sensitization Threshold

ECHA - European Chemicals Agency

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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
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
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Significant - Statistically significant difference in reported results as compared to controls with a $p < .05$ 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 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 use of this material under current conditions is supported by existing information.

Dodecanenitrile was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that dodecanenitrile is not genotoxic and provided a calculated MOE >100 for the repeated dose, developmental and reproductive toxicity endpoints. Data from read-across analogs 2-methyldecanenitrile (CAS # 69300-15-8) and 3,7-dimethyloctanenitrile (CAS # 40188-41-8) show that dodecanenitrile is not a safety concern at the current, declared levels of use for the skin sensitization endpoint. The local respiratory toxicity endpoint was completed using the TTC for a Cramer Class III material and the exposure to dodecanenitrile was below the TTC (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; dodecanenitrile is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, dodecanenitrile was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (ECHA REACH Dossier: dodecanenitrile)

Repeated Dose Toxicity: NOEL = 16.7 mg/kg/day. (ECHA REACH Dossier: dodecanenitrile)

Developmental and Reproductive Toxicity: NOAEL = 250 mg/kg/day. (ECHA REACH Dossier: dodecanenitrile)

Skin Sensitization: Not a concern for skin sensitization. (RIFM, 2004; RIFM, 2009c; RIFM, 2010a)

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: Critical Measured Value: 89% (OECD 301F) (RIFM, 1997a)

Bioaccumulation: Screening-Level: 24.3 L/kg (US EPA, 2012a)

Ecotoxicity: Screening-Level: *Daphnia magna* 48-h LC50: 0.358 mg/L (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: *Daphnia magna* 48-h LC50: 0.358 mg/L (US EPA, 2012a)
RIFM PNEC is: 0.0358 µg/L
●Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe <1

1. Identification

1. **Chemical Name**: Dodecanenitrile
2. **CAS Registry Number**: 2437-25-4
3. **Synonyms**: 1-Cyanoundecane; Dodecanonitrile; Lauric acid nitrile; Dodecyl nitrile; Clonal; アルキル（又はアルケニル，C = 8 ~ 18）ニトリル; Lauronitrile; Dodecanenitrile
4. **Molecular Formula**: $C_{12}H_{23}N$
5. **Molecular Weight**: 181.23
6. **RIFM Number**: 5277

2. Physical data

1. **Boiling Point:** 277.28 °C (US EPA, 2012a)
2. **Flash Point:** 201.00 °F. TCC (93.89 °C)*
3. **Log K_{ow}**: 5.8 at 35 °C (RIFM, 1997b), 4.77 (US EPA, 2012a)
4. **Melting Point**: 24.68 °C (US EPA, 2012a)
5. **Water Solubility:** 2.51 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.81900 to 0.82700 @ 25.00 °C; 0.82000 to 0.82800 @ 20.00 °C*
7. **Vapor Pressure:** 0.00382 mmHg @ 20 °C (US EPA, 2012a), 0.00628 mmHg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** Colorless clear liquid with a medium-dry, citrus, orange peel, metallic, spicy odor.

*http://www.thegoodscentscompany.com/data/rw1004961.html#toorgano, retrieved 3/24/2017.

3. Exposure

1. **Volume of Use (Worldwide Band):** 10–100 metric tons (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.016% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00016 mg/kg/day or 0.012 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00061 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015, 2017; Comiskey et al., 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**: None
   c. **Developmental and Reproductive Toxicity**: None
   d. **Skin Sensitization**: 2-Methyldecanenitrile (CAS # 69300-15-8) and 3,7-dimethyloctanenitrile (CAS # 40188-41-8)
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity**: None
3. **Read-across Justification**: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Dodecanenitrile is reported to occur in the following food* but it is not found in natural complex substances (NCS):
Chicken.
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 contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Available; accessed on 03/24/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, dodecanenitrile does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of dodecanenitrile was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance to OECD TG471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 and *Escherichia coli* strain WP2

uvrA were treated with dodecanenitrile in DMSO (dimethyl sulfoxide) at the concentrations up to 10000 μg/plate in the presence and absence of metabolic activation. No increase in the number of revertant colonies was observed at the concentrations tested (ECHA REACH Dossier: dodecanenitrile). Under the conditions of the study, dodecanenitrile was considered not mutagenic in the Ames test.

The clastogenic activity of dodecanenitrile was assessed in an *in vitro* chromosome aberration assay conducted in compliance with GLP regulations and in accordance with OECD 473. Chinese hamster lung fibroblasts (V79 cells) were exposed to dodecanenitrile in acetone at the following concentrations: without S9-mix, 4 h μg/mL: 1.6, 3.1, 6.3, 12.5, 25.0, 50.0 μg/mL, and with S9-mix, 4 h μg/mL: 57.8, 115.6, 231.3, 462.5, 925.0, 1850.0. In a second experiment, the concentrations were: without S9-mix, 18 h μg/mL: 0.8, 1.6, 3.1, 6.3, 12.5, 25.0; without S9-mix, 28 h μg/mL: 3.1, 6.3, 12.5, 25.0, 50.0, 75.0; with S9-mix, 4 h μg/mL: 57.8, 115.6, 231.3, 462.5, 925.0, 1850.0 μg/mL. No biologically relevant increase in the frequencies of polyploid metaphases was observed after treatment with the test material as compared to the frequencies of the controls (ECHA REACH Dossier: dodecanenitrile). Under the conditions of the study, dodecanenitrile was considered to be non-clastogenic to mammalian cells.

Based on the available data, dodecanenitrile does not present a concern for genotoxic potential.

Additional References: RIFM, 2008; RIFM, 2009a; RIFM, 2013.

Literature Search and Risk Assessment Completed On: 03/15/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for dodecanenitrile is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on dodecanenitrile for the repeated dose toxicity endpoint. An OECD 422 study was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered via gavage test material, dodecanenitrile at doses of 0, 50, 250, or 1000 mg/kg/day in 2% methylcellulose. Dodecanenitrile was administered to the male rats for at least 28 days and to the female rats for 14 days prior to mating, through the pre-mating, mating, and gestation periods until the F1 generation reached day 4 postpartum. Mortality and alteration in clinical signs were reported among the high-dose group females. Alterations in clinical signs were also reported among the high-dose males and mid-dose females. Hematological alterations were reported among the high-dose males; however, the significance remained unknown. During gross necropsy, the high-dose males were reported to have an enlarged liver (6/10) and a reduction in thymus size (3/10). The high-dose females were reported to have an enlarged liver, stomach with discolorations, crateriform retractions and foci, and enlarged adrenal glands. The high-dose males had a significant increase in the absolute and relative liver weights. Histopathological examination revealed minimal-to-moderate, centrilobular-to-diffuse hepatocellular hypertrophy and atrophy/involution in the thymus among the high-dose group males. The mid- and high-dose males showed ulceration, erosion, and mucosal necrosis in the forestomach and glandular stomach. The high-dose male kidneys showed an increase in tubular basophilia. The 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 the mid- and high-dose females. Ulceration was also reported to occur in the duodenum of the high-dose females. Thus, the NOEL was considered to be 50 mg/kg/day, based on gross pathological alterations associated with histopathology in the GI tract and liver, along with clinical signs among the males and females of higher-dose groups and mortality among the high-dose group females (ECHA REACH Dossier: dodecanenitrile).

A default safety factor of 3 was used when deriving a NOEL from an OECD 422 study. The safety factor has been approved by The Expert Panel for Fragrance Safety*.

Thus, the derived NOEL for the repeated dose toxicity data is 50/3 or 16.7 mg/kg/day.

Therefore, the dodecanenitrile MOE for the repeated dose toxicity endpoint can be calculated by dividing the dodecanenitrile NOEL in mg/kg/day by the total systemic exposure to dodecanenitrile, 16.7/0.00061 or 27377.

In addition, the total systemic exposure to dodecanenitrile (0.61 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 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: 3/20/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for dodecanenitrile is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on dodecanenitrile for the developmental and reproductive toxicity endpoints. An OECD 422 study was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered dodecanenitrile via gavage test material at doses of 0, 50, 250, or 1000 mg/kg/day in 2% methylcellulose. Dodecanenitrile was administered to the male rats for at least 28 days and to the female rats for 14 days prior to mating, through the pre-mating, mating, and gestation periods until the F1 generation reached day 4 postpartum. Mortality and alterations in clinical signs were reported among the high-dose females. The mid-dose females and high-dose males also showed alterations in clinical signs, but there were no alterations in the male or female reproductive function up to the highest dose tested. Secondary to parental toxicity, reduced open-field activity and reduced locomotor activity, reduced body temperature (only males), increased incidence of post-implantation loss, reduced mean litter size, increased incidence of dead pups at first litter check, and increased incidence of postnatal loss were observed at the highest dose. Sex ratios at first litter check and on day 4 postpartum were unaffected by treatment. Mean pup weight on day 0 postpartum and mean pup weight developments were reduced at 1000 mg/kg/day. Thus, the NOAEL for developmental and reproductive toxicity was considered to be 250 mg/kg/day, based on mortality and the poor health conditions of the females at the highest dose. (ECHA REACH Dossier: dodecanenitrile). **Therefore, the dodecanenitrile MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the dodecanenitrile NOAEL in mg/kg/day by the total systemic exposure to dodecanenitrile, 250/0.00061 or 409836.**

In addition, the total systemic exposure to dodecanenitrile (0.61 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/20/2017.

10.1.4. Skin sensitization

Based on the existing data and read-across 2-methyldecanenitrile (CAS # 69300-15-8) and 3,7-dimethyloctanenitrile (CAS # 40188-41-8), dodecanenitrile does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for dodecanenitrile. Based on the existing data and read-across 2-methyldecanenitrile (CAS # 69300-15-8) and 3,7-dimethyloctanenitrile (CAS # 40188-41-8; see Section 5), dodecanenitrile does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), read-across material 2-methyldecanenitrile was found to be non-sensitizing up to 100% (RIFM, 2009c). Similarly, another read-across material, 3,7-dimethyloctanenitrile, did not induce contact sensitization up to 30% (7500 μg/cm^2) in an LLNA (RIFM, 2004). In a maximization and a Buehler test in guinea pigs, read-across material 2-methyldecanenitrile did not present reactions indicative of sensitization (RIFM, 1989a; RIFM, 1982). Similarly, another read-across material, 3,7-dimethyloctanenitrile, did not induce contact sensitization in a Buehler test (RIFM, 1988). In a confirmatory human repeat insult patch test (HRIPT), 0.75% or 581 μg/cm^2 of dodecanenitrile did not present reactions indicative of sensitization in 39 subjects (RIFM, 1965). In an HRIPT conducted with 2% or 1000μg/cm^2 read-across 3,7-dimethyloctanenitrile in alcohol SDA 39C, no reactions were observed (RIFM, 1989b). Additionally, in an HRIPT with 2250 μg/cm^2 of read-across material 2-methyldecanenitrile, no reactions indicative of sensitization were observed in any of the 101 volunteers (RIFM, 2010a). Based on a WOE from structural analysis, human study, and read-across materials 2-methyldecanenitrile and 3,7-dimethyloctanenitrile, dodecanenitrile does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/23/2016.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, dodecanenitrile 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 dodecanenitrile in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of absorbance, dodecanenitrile does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/28/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level of the material dodecanenitrile 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 dodecanenitrile. Based on the Creme RIFM Model, the inhalation exposure is 0.012 mg/day. This exposure is 39.2 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: 3/21/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of dodecanenitrile was performed following the RIFM Environmental Framework (Salvito et al., 2002; #40315), which provides 3 tiers of screening level 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, dodecanenitrile 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 dodecanenitrile as possibly being either persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015; #68218). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2016). 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., USEPA'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.

10.2.2. Risk assessment

Based on current Volume of Use (2011), dodecanenitrile presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 1994: The ready biodegradability of the test material was determined using a CO_2 production test based on OECD Guideline 301B. The biodegradation rate of dodecanenitrile was 75.4% (66.1%–84.8%).

RIFM, 1997a: The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F method. Dodecanenitrile at 100 mg/L underwent 89% biodegradation after 28 days.

10.2.3.2. Ecotoxicity. No data available.

10.2.4. Other available data

Dodecanenitrile has been registered under REACH but no additional data is available.

10.2.5. 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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.121 mg/L			1,000,000	0.000121 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.489 mg/L	0.358 mg/L	0.767 mg/L	10,000	0.0358 µg/L	Aldehydes (Mono)

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

Exposure	Europe (Eu)	North America (NA)
Log K_{ow} Used	5.8	5.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
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 0.0358 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: 3/14/17.

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/ntp_tox/index.cfm
- **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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2018.01.005.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2018.01.005.

Appendix

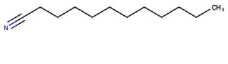
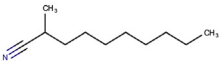
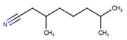
Read-across justification

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 was 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™ v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification predictions were generated using OECD QSAR Toolbox 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	Read-across material
Principal Name	Dodecanenitrile	2-Methyldecanenitrile	3,7-Dimethyloctanenitrile
CAS No.	2437-25-4	69300-15-8	40188-41-8
Structure			
Similarity (Tanimoto score)		0.89	0.785
Read-across Endpoint		• Skin Sensitization	• Skin Sensitization
Molecular Formula	$C_{12}H_{23}N$	$C_{11}H_{21}N$	$C_{10}H_{19}N$
Molecular Weight	181.32	167.30	153.27
Melting Point (°C, EPI Suite)	24.68	11.56	−10.09
Boiling Point (°C, EPI Suite)	277.28	250.43	221.27
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.838	3.55	16.4
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	5.8[a]	4.2[b]	3.4[c]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	2.51	8.892	31.28
J_{max} (mg/cm^2/h, SAM)	2.383	5.830	12.490
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.26E+001	3.96 + 001	2.95E-004
Skin Sensitization			
Protein binding by OASIS v1.1	• No alert found	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found	• No alert found
Skin Sensitization Model (CAESAR) (version 2.1.6)	• Sensitizer (low reliability)	• Sensitizer (low reliability)	• Sensitizer (low reliability)
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See supplemental data 1	See supplemental data 2	See supplemental data 3

[a] RIFM, 1997b.
[b] RIFM, 2009b.
[c] RIFM, 2010b.

Summary:

There are insufficient toxicity data on the target material dodecanenitrile (CAS # 2437-25-4). 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, analogs 2-methyldecanenitrile (CAS # 69300-15-8) and 3,7-dimethyloctanenitrile (CAS # 40188-41-8) were identified as a read-across material with data for its respective toxicological endpoints.

Conclusion/Rationale:

- 2-Methyldecanenitrile (CAS # 69300-15-8) was used as a read-across analog for target material dodecanenitrile (CAS # 2437-25-4) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of saturated aliphatic nitriles.
  - o The target substance and the read-across analog share a decanenitrile fragment.
  - o The key difference between the target substance and the read-across analog is that the read-across analog is substituted with a methyl group on the alpha carbon and the target lacks this substitution. This structural difference between the target substance and the read-across analog does not affect consideration of the toxicological endpoint.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoint.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.

- o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- o The target substance and the read-across analog are predicted to be sensitizers by the CAESAR model for skin sensitization. There are no other protein binding alerts for skin sensitization for either of the substances. The data described in the skin sensitization section show that the read-across analog does not present a concern for skin sensitization. Therefore, the prediction will be superseded by the available data.
- o The target substance 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.

- 3,7-Dimethyloctanenitrile (CAS # 40188-41-8) was used as a read-across analog for target material dodecanenitrile (CAS # 2437-25-4) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of saturated aliphatic nitriles.
  - o The target substance and the read-across analog have a saturated nitrile fragment in common.
  - o The key difference between the target substance and the read-across analog is that the read-across analog is branched saturated nitrile while the read-across analog is straight chain aliphatic nitrile. This structural difference between the target substance and the read-across analog does not affect consideration of the toxicological endpoint.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoint.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 40\%$ for the target substance and $\leq 80\%$ for the read-across analog. While percentage 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.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are predicted to be sensitizers by the CAESAR model for skin sensitization. There are no other protein binding alerts for skin sensitization for either of the substances. The data described in the skin sensitization section shows that the read-across analog does not present a concern for skin sensitization. Therefore, the prediction will be superseded by the available data.
  - o The target substance 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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