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Short review

RIFM fragrance ingredient safety assessment, cuminyl nitrile, CAS Registry Number 13816-33-6

A.M. Api [a, *], D. Belsito [b], D. Botelho [a], D. Browne [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], P. Calow [f], M.L. Dagli [g], M. Date [a], W. Dekant [h], C. Deodhar [a], A.D. Fryer [i], K. Joshi [a], S. La Cava [a], A. Lapczynski [a], D.C. Liebler [j], D. O'Brien [a], R. Parakhia [a], A. Patel [a], T.M. Penning [k], G. Ritacco [a], J. Romine [a], D. Salvito [a], T.W. Schultz [l], I.G. Sipes [m], Y. Thakkar [a], S. Tsang [a], J. Wahler [a]

[a] Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA
[b] Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA
[c] Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo SE-20502, Sweden
[d] Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA
[e] Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany
[f] Member RIFM Expert Panel, Humphrey School of Public Affairs, University of Minnesota, 301 19th Avenue South, Minneapolis, MN 55455, USA
[g] Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo CEP 05508-900, Brazil
[h] Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany
[i] Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA
[j] Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN 37232-0146, USA
[k] Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA 19104-3083, USA
[l] Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996- 4500, USA
[m] Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, USA

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1. Identification

1. **Chemical Name**: Cuminyl nitrile
2. **CAS Registry Number**: 13816-33-6
3. **Synonyms:** Benzonitrile, 4-(1-methylethyl)-; Cuminyl nitrile; 4-Isopropylbenzonitrile; Cumin nitrile
4. **Molecular Formula**: $C_{10}H_{11}N$
5. **Molecular Weight**: 145.21
6. **RIFM Number**: 1107

2. Physical data

1. **Boiling Point:** 237.48 °C [EPI Suite]
2. **Flash Point**: 94 °C [GHS]
3. **Log K_{OW}**: 2.6 [RIFM, 2010], 3 [EPI Suite]
4. **Melting Point**: 21.62 °C [EPI Suite]
5. **Water Solubility:** 119.5 mg/L [EPI Suite]
6. **Specific Gravity**: Not Available
7. **Vapor Pressure:** 0.034 mmHg @ 20 °C [EPI Suite 4.0], 0.0529 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar extinction coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** A pale yellow to yellow clear liquid with a medium spicy, cumin, dry, green odor while at 1% or less in dipropylene glycol.*

* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

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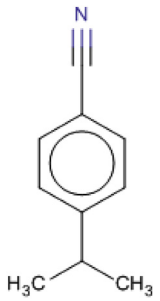
0278-6915/

Version: 022317. This version replaces any previous versions.
Name: Cuminyl nitrile
CAS Registry Number: 13816-33-6



Abbreviation 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) 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
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
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

*http://www.thegoodscentscompany.com/data/rw1016811.html#toorgano, retrieved 1/14/2016.

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.0025% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000023 mg/kg/day or 0.0016 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00018 mg/kg/day (RIFM, 2016)

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

**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).

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
2. **Analogues Selected**:

   a. **Genotoxicity:** Benzonitrile (CAS # 100-47-0)
   b. **Repeated Dose Toxicity:** Benzonitrile (CAS # 100-47-0)
   c. **Developmental and Reproductive Toxicity**: None

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 reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across material benzonitrile (CAS # 100-47-0) show that this material is not genotoxic, provided a MOE > 100 for the repeated dose toxicity endpoint and is below the non-reactive DST for the skin sensitization endpoint. The developmental and reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.0015, 0.0015 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic (RIFM, 2015; RIFM, 2007)

Repeated Dose Toxicity: NOAEL = 37.5 mg/kg/day (ECHA, REACH Dossier on benzonitrile)

Developmental and Reproductive Toxicity: No data available. Exposure is below the TTC.

Skin Sensitization: Not a sensitization concern. Exposure is below DST.

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening Level: 2.7 (Biowin 3) (EpiSuite ver 4.1)

Bioaccumulation: Screening Level: 44 L/kg (EpiSuite ver 4.1)

Ecotoxicity: Screening Level: Fish LC50: 58.88 mg/L (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 58.88 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.05888 μg/L

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; Cleared at screening level

Expert judgment	Toxtree v 2.6	OECD QSAR toolbox v 3.2
III	III	III

d. **Skin Sensitization:** Benzonitrile (CAS# 100-47-0)
e. **Phototoxicity/Photoallergenicity**: None
f. **Local Respiratory Toxicity**: None
g. **Environmental Toxicity**: None

3. **Read-across Justification**: See Appendix below

6. Metabolism

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

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

Cuminyl nitrile is not reported to occur in food 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, 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 7/13/2016.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, cuminyl nitrile does not present a concern for genetic toxicity.

10.1.2. Risk assessment

Cuminyl nitrile was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013a,b). The mutagenic activity of cuminyl nitrile (CAS # 13816-33-6) 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/preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and *Escherichia coli* strains WP2uvrA were treated with cuminyl nitrile in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2015). Under the conditions of the study, cuminyl nitrile was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of cuminyl nitrile however, read across can be made to benzonitrile (CAS # 100-47-0; see Section 5). In an *in vitro* chromosomal aberration study (ECHA dossier: benzonitrile, accessed 06/27/2016),

benzonitrile produced a weakly positive response (11% increase vs 3% increase in vehicle control) in the presence of metabolic activation, but this increase was not dose dependent and thus was not considered to be biologically relevant. Furthermore, an *in vivo* micronucleus study showed negative results for clastogenicity. Benzonitrile was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral route, to groups of male and female NMRI mice (5/sex/dose). Doses of 250, 500, or 1000 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h post treatment period, the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2007). Under the conditions of the study, benzonitrile was not considered to be clastogenic in the *in vivo* micronucleus test, and this can be extended to cuminyl nitrile.

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

Additional References: Zeiger et al., 1988; Osgood and Cyr, 1998; Bonacker et al., 2004; RIFM, 2009; Wu et al., 2009; RIFM, 2013a,b.

Literature Search and Risk Assessment Completed on: 06/27/2016.

10.1.3. Repeated dose toxicity

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

10.1.4. Risk assessment

There are no repeated dose toxicity data on cuminyl nitrile. Read across material benzonitrile (CAS# 100-47-0; see Section 5) has sufficient repeated dose toxicity data. A 13 week gavage study was conducted with test material, benzonitrile administered to a group of 10 Fischer 344 rats/sex/group at doses of 0 (corn oil), 19, 37.5, 75, 150 and 300 mg/kg/day. Hyperactivity and aggressiveness was reported among the 150 and 300 mg/kg/day animals. Hind leg strength was also reduced along with delayed response to thermal stimuli among the high dose females. The kidney weight was increased in males of the 75 mg/kg/day and higher groups. The NOAEL was determined to be 37.5 and 75 mg/kg/day for females and males respectively (ECHA, REACH Dossier on benzonitrile). In another study, a 13 week gavage toxicity study was conducted with test material, benzonitrile administered to a group of 10 B6C3F1/sex/group at doses of 0 (corn oil), 0, 37.5, 75, 150, 300, 600 mg/kg. Females of the high dose group showed startled responses to acoustic signals. A significant reduction in body weight gain was reported among the high dose animals. Liver weights among the animals treated with 75 mg/kg/day and higher were significantly higher than controls. Centrilobular hypertrophy of liver cells, increase of Kupffer cells, mineralization and cell necrosis was reported among the 300 and 600 mg/kg/day treated males and the 600 mg/kg/day treated females. Thus the NOAEL was determined to be 37.5 mg/kg/day both for males and females (ECHA, REACH Dossier on benzonitrile). The most conservative NOAEL of 37.5 mg/kg/day was selected for the repeated dose toxicity endpoint. **Therefore, the MOE can be calculated by dividing the benzonitrile NOAEL by the total systemic exposure for cuminyl nitrile, 37.5/0.00018 or 208333.**

In addition, the total systemic exposure for cuminyl nitrile (0.18 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

Additional References: ECHA, REACH Dossier on Benzonitrile.

Literature Search and Risk Assessment Completed on: 7/6/2016.

10.1.5. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on cuminyl nitrile or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC) at the current level of use.

10.1.6. Risk assessment

There are no developmental or reproductive toxicity data on cuminyl nitrile or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure for cuminyl nitrile (0.18 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) at the current level of use for the developmental and reproductive toxicity endpoints.

Additional References: ECHA, REACH Dossier on benzonitrile.

Literature Search and Risk Assessment Completed on: 7/6/2016.

10.1.7. Skin sensitization

Based on the existing data and application of DST, cuminyl nitrile does not present a concern for skin sensitization.

10.1.8. Risk assessment

Limited skin sensitization studies are available on cuminyl nitrile. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Toxtree 2.6.6; OECD toolbox v3.3). There exist no predictive test on this chemical or any of its possible read across materials. However, in confirmatory human maximization tests 1% (690) cuminyl nitrile and 2% (1380 μg/cm^2) read across material benzonitrile (CAS# 100-47-0; See Section 5) did not result in sensitization reactions (RIFM, 1980; RIFM, 1977). Acting conservatively, due to limited data on read across, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900μg/cm^2. Utilizing 900μg/cm^2 for cuminyl nitrile, the application of the Quantitative Risk Assessment (QRA) described by Api et al. (2008) results in the acceptable exposure limits summarized in Table 1. The current 95th percentile dermal exposure is below the DST for non-reactive materials when evaluated in all QRA categories. Based on application of DST, cuminyl nitrile does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/11/16.

10.1.9. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, cuminyl nitrile would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 1
Acceptable exposure limits for cuminyl nitrile based on DST non-reactive –

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

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

10.1.10. Risk assessment

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

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/29/16.

10.1.11. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, cuminyl nitrile, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.12. Risk assessment

There are no inhalation data available on cuminyl nitrile. Based on the Creme RIFM model, the inhalation exposure is 0.0016 mg/day. This exposure is 293.8 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: 07/08/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of cuminyl nitrile was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, cuminyl nitrile 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 EPISUITE ver 4.1 did not identify cuminyl nitrile as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

10.2.2. Risk assessment

Based on current Volume of Use (2011), cuminyl nitrile does not present a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.3. Other available data

Cuminyl nitrile has been pre-registered for REACH with no additional data at this time.

10.2.4. 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.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	<u>58.88 mg/L</u>			1,000,000	0.05888μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.6	2.6
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 0.05888 μg/L. The revised PEC/PNECs for EU and NA: not applicable; cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 6/20/2016.

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://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww%26ei=KMSoUpiQK-arsQS324GwBg%26ved=0CBQQ1S4

*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.2017.04.042.

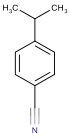
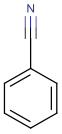
Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.04.042.

Appendix

Methods

- The identified read across analogue were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints. (Rogers and Hahn, 2010).
- The physicochemical properties of the target substance and the read across analogue were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Skin sensitization was estimated using CAESAR v. 2.1.6 (Cassano et al., 2010).
- Protein binding was estimated 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).
- Strategies on finding and using read across are described in Schultz et al., 2015.

	Target material	Read across material
Principal Name	Cuminyl nitrile	Benzonitrile
CAS No.	13816-33-6	100-47-0
Structure		
Similarity (Tanimoto score)		0.67857
Read across endpoint		• Genotoxicity, • Repeated dose, • Skin sensitization
Molecular Formula	$C_{10}H_{11}N$	C_7H_5N
Molecular Weight	145.21	103.12
Melting Point (°C, EPISUITE)	21.62	−7.49
Boiling Point (°C, EPISUITE)	237.48	191.43
Vapor Pressure (Pa @ 25 °C, EPISUITE)	7.05	74.8
Log Kow (KOWWIN v1.68 in EPISUITE)	3.00	1.56
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	119.5	2893
J_{max} (mg/cm^2/h, SAM)	11.02809	101.9247
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.03E+001	5.27E+000
Genotoxicity		
DNA binding (OASIS v 1.1 QSAR Toolbox 3.4)	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
In-vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found
In-vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Repeated dose toxicity		

(*continued*)

	Target material	Read across material
Repeated Dose (HESS)	• Not categorized	• Not categorized
Sensitization		
Protein binding by OASIS v1.4	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found
Protein binding potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein binding alerts for skin sensitization by OASIS v1.4	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (low reliability)	• Sensitizer (low reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on cuminyl nitrile (CAS # 13816-33-6). Hence *in-silico* evaluation was conducted by determining suitable read across analogues for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogue benzonitrile (CAS # 100-47-0) was identified as a read across material with data for its respective toxicity endpoints.

Conclusion/Rationale

- Benzonitrile (CAS # 100-47-0) could be used as structurally similar read across analogue for the target material cuminyl nitrile (CAS # 13816-33-6) for the gentoxicity, repeated dose, and skin sensitization toxicological endpoints.
  - The target substance and the read across analogue are structurally similar and belong to the structural class of benzonitriles.
  - The key difference between the target substance and the read across analogue is that the target has an aliphatic group (isopropyl) substitution on the para position while the read across does not. The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.
  - The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the benzonitrile fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxic endpoint perspective.
  - The target substance and the read across analogue have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for the genotoxicity, repeated dose, and skin sensitization endpoints.
  - According to the QSAR OECD Toolbox (V3.4), structural alerts for genotoxicity, repeated dose, and skin sensitization endpoints are consistent between the target substance and the read across analogue as seen in the table above.
  - The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.
  - The structural alerts for genotoxicity, repeated dose, and skin sensitization endpoints are consistent between the metabolites of the read across analogue and the target substance.
  - The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

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