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RIFM fragrance ingredient safety assessment, 3-methyl-5-phenylpent-2-enenitrile, CAS registry number 93893-89-1

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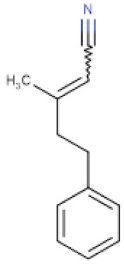
Name: 3-Methyl-5-phenylpent-2-enenitrile
CAS Registry Number: 93893-89-1
Additional CAS Numbers*:
53243-60-0 (E)-3-Methyl-5-phenylpent-2-enenitrile
53243-59-7 (Z)-3-Methyl-5-phenylpent-2-enenitrile
*Included because the materials are isomers.



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(*continued*)

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
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.

3-Methyl-5-phenylpent-2-enenitrile was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3-methyl-5-phenylpent-2-enenitrile is not genotoxic. Data on 3-methyl-5-phenylpent-2-enenitrile provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive toxicity and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 3-methyl-5-phenylpent-2-enenitrile is below the TTC (0.0015 mg/kg/day and 0.47 mg/day, respectively). Data from 3-methyl-5-phenylpent-2-enenitrile provided a No Expected Sensitization Induction Level (NESIL) of 270 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible spectra (UV/Vis) spectra; 3-methyl-5-phenylpent-2-enenitrile is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-methyl-5-phenylpent-2-enenitrile 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.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2007d; RIFM, 2008a)
Repeated Dose Toxicity: NOAEL = 16.7 mg/kg/day. (RIFM, 2015e)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 270 μg/cm^2. RIFM (2008b)
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:
Critical Measured Value: 38% (OECD 301D) for CAS # 93892-89-1 RIFM (2000)

Bioaccumulation:

(*continued on next page*)

(*continued*)

Screening-level: 77.47 L/kg **Ecotoxicity:** Critical Ecotoxicity Endpoint: 72-h Algae EyC50: 3.44 mg/L for CAS # 93892-89-1 **Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards	(EPI Suite v4.11; US EPA, 2012a) RIFM (2016b)
Risk Assessment: **Screening-level:** PEC/PNEC (North America and Europe) > 1 **Critical Ecotoxicity Endpoint:** 72-h Algae EyC50: 3.44 mg/L for CAS # 93892-89-1 **RIFM PNEC is:** 3.44 μg/L • **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1	(RIFM Framework; Salvito et al., 2002) RIFM (2016b)

1. Identification

Chemical Name: 3-Methyl-5-phenylpent-2-enenitrile **CAS Registry Number:** 93893-89-1 **Synonyms:** Citronitrile; 2-Pentenenitrile, 3-methyl-5-phenyl- (isomer unspecified); Reaction mass of (E)-3-methyl-5-phenylpent-2-enenitrile and (Z)-3-methyl-5-phenylpent-2-enenitrile; 3-Methyl-5-phenylpent-2-enenitrile **Molecular Formula:** $C_{12}H_{13}N$ **Molecular Weight:** 171.24 **RIFM Number:** 5541 **Stereochemistry:** Isomer not specified. One geometric center present and 2 total geometric isomers possible.	Chemical Name: (Z)-3-Methyl-5-phenylpent-2-enenitrile **CAS Registry Number:** 53243-59-7 **Synonyms:** 3-Methyl-5-phenylpent-2-enenitrile; 2-Pentenenitrile, 3-methyl-5-phenyl-, (Z)- **Molecular Formula:** $C_{12}H_{13}N$ **Molecular Weight:** 171.24 **RIFM Number:** 5724 **Stereochemistry:** Z isomer specified. One geometric center present and 2 total isomers possible.	Chemical Name: (E)-3-Methyl-5-phenylpent-2-enenitrile **CAS Registry Number:** 53243-60-0 **Synonyms:** 3-Methyl-5-phenylpent-2-enenitrile; 2-Pentenenitrile, 3-methyl-5-phenyl-, (E)- **Molecular Formula:** $C_{12}H_{13}N$ **Molecular Weight:** 171.24 **RIFM Number:** 5725 **Stereochemistry:** E isomer specified. One geometric center present and 2 total isomers possible.

2. Physical data*

1. **Boiling Point:** 296.2 °C at 1013 hPa (RIFM, 2015b), 297.16 °C (EPI Suite)
2. **Flash Point:** 0.49% at pH 4, 0.75% at pH 7, 1.48% at pH 9 at 50 °C and 120 h (RIFM, 2015d), 146.5 °C (RIFM, 2015c), 142 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.37 (EPI Suite), 2.93 at 23.6 °C (weighted mean); 2.81 and 2.98 (isomer 1 and 2, respectively, with area % of 32.5 and 67.5%, respectively) (Symrise, 2016ad)
4. **Melting Point**: 33.12 °C (EPI Suite)
5. **Water Solubility:** 43.83 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00192 mm Hg at 25 °C (EPI Suite), 0.00105 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

*Physical data is identical for all materials included in this assessment.

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.010% (RIFM, 2018)
2. **Inhalation Exposure**:** 0.00037 mg/kg/day or 0.028 mg/day (RIFM, 2018)
3. **Total Systemic Exposure***:** 0.0013 mg/kg/day (RIFM, 2018)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

**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:** 50.2%

RIFM, 2015a: An *in vitro* human skin permeation rate and distribution study was conducted on (2E)-3-methyl-5-phenylpent-2-enenitrile (MPE). Applications were made with the test material (5 μL/cm^2 containing 49.9 μg/cm^2) in 70/30 (v/v) ethanol/water under both unoccluded and occluded conditions at a target concentration of 1% (measured concentration 0.997% [w/v]). Twelve active dosed diffusion cells were prepared for both unoccluded and occluded conditions in addition to 4 control cells (1 per donor, unoccluded). Epidermal membranes (4 donors, female abdominal skin) were used, and integrity was assessed by measuring electrical resistance. Permeation of MPE, from a 5 μL/cm^2 dose of a 0.997% (w/v) donor solution in 70% ethanol, was measured at 12 time points over 24 h using a 25/75 (v/v) ethanol/pH 7.4 phosphate-buffered saline receptor phase. For the occluded group, donor chambers were occluded using greased glass coverslips applied immediately following application. At 24 h, the epidermal membranes were wiped, the tape was stripped 10 times, and the MPE content of the wipes, strips, and remaining epidermis was determined. Filter paper skin supports were extracted, and diffusion cell donor chambers and glass coverslips (for the occluded group) were wiped to remove sealing grease

and then washed. These samples were analyzed so that mass balance could be performed. Evaporative loss of MPE was estimated by measuring the loss from PTFE sheets under the same unoccluded conditions. Sensitive UHPLC-UV methods were developed for MPE. There were 2 MPE peaks due to the presence of 2 isomers. These were identified as MPE peak A (30.4% by peak area, likely (Z)-isomer) and MPE peak B (69.6% by peak area, predominant (E)-isomer). The isomer ratio was used to calculate the combined total MPE as a weighted average. This was necessary because the 2 isomers performed differently in terms of skin penetration (greater for MPE peak B) and evaporative loss (greater for MPE peak A). At 24 h, 15.3 ± 1.6 and 23.9 ± 1.4 μg/cm^2 of total MPE had permeated under unoccluded and occluded conditions, respectively, corresponding to 30.8 ± 3.3% and 48.0 ± 2.8% of the applied dose. Overall recoveries of the applied MPE were low under unoccluded conditions due to evaporative loss (42.5 ± 2.9% of the applied dose) and higher under occluded conditions (89.9 ± 0.5%). The investigation of evaporative loss from PTFE sheet mounted in diffusion cells showed that evaporation of the fragrance material was relatively slow, but still substantial (combined total MPE; 38% recovered at 24 h). The overall skin absorption values, defined as amounts that have permeated and amounts in the epidermis (excluding tape strips) and skin support, were 16.2 ± 1.7 and 25.0 ± 1.4 μg/cm^2, for the unoccluded and occluded groups, respectively, corresponding to 32.4 ± 3.4% and 50.2 ± 2.8% of the applied dose.

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

6. Computational toxicology evaluation

6.1. Cramer classification

Class III, High

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

6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below

7. Metabolism

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

8. Natural occurrence

3-Methyl-5-phenylpent-2-enenitrile, (Z)-3-methyl-5-phenylpent-2-enenitrile, and (E)-3-methyl-5-phenylpent-2-enenitrile are 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 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 for 3-methyl-5-phenylpent-2-enenitrile; accessed on 09/23/21; (Z)-3-methyl-5-phenylpent-2-enenitrile, and (E)-3-methyl-5-phenylpent-2-enenitrile are pre-registered for 2010; no dossiers available as of 09/23/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 3-methyl-5-phenylpent-2-enenitrile are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.021
2	Products applied to the axillae	0.0062
3	Products applied to the face/body using fingertips	0.12
4	Products related to fine fragrances	0.12
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.029
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.029
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.029
5D	Baby cream, oil, talc	0.0097
6	Products with oral and lip exposure	0.065
7	Products applied to the hair with some hand contact	0.24
8	Products with significant ano-genital exposure (tampon)	0.0097
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.23
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.81
10B	Aerosol air freshener	0.81
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0097
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	65

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 3-methyl-5-phenylpent-2-enenitrile, the basis was the reference dose of 0.167 mg/kg/day, a skin absorption value of 50.2%, and a skin sensitization NESIL of 270 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 3-methyl-5-phenylpent-2-enenitrile does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 3-Methyl-5-phenylpent-2-enenitrile was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 3-methyl-5-phenylpent-2-enenitrile 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 TA98, TA100, TA1535, TA1537, and TA102 were treated with 3-methyl-5-phenylpent-2-enenitrile in solvent 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, 2007d). Under the conditions of the study, 3-methyl-5-phenylpent-2-enenitrile was not mutagenic in the Ames test.

The clastogenic activity of 3-methyl-5-phenylpent-2-enenitrile 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 gavage to groups of male and female NMRI mice. Doses of 125, 250, and 500 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2008a). Under the conditions of the study, 3-methyl-5-phenylpent-2-enenitrile was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 3-methyl-5-phenylpent-2-enenitrile does not present a concern for genotoxic potential.

Additional References: RIFM, 2009; RIFM, 2013a; RIFM, 2007e; RIFM, 2007b.

Literature Search and Risk Assessment Completed On: 06/09/21.

11.1.2. Repeated dose toxicity

The MOE for 3-methyl-5-phenylpent-2-enenitrile is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 3-methyl-5-phenylpent-2-enenitrile to support the repeated dose toxicity endpoint. An OECD 407/GLP oral gavage subchronic toxicity study was conducted in Sprague Dawley rats. Groups of 5 rats/sex/dose were administered 3-methyl-5-phenylpent-2-enenitrile (Citronitrile) via oral gavage at doses of 0, 10, 50, or 250 mg/kg/day in corn oil for 28 days. There was a statistically significant decrease in body weight among animals of the high-dose group throughout the study, which was associated with decreased food consumption. The mean body weight for males and females at this high dose was 20.6% and 16.7% below the control group, respectively, by week 4. There were statistically significant decreases in behavioral open-field parameters (ambulatory counts and vertical counts) observed in males of the 250 mg/kg/day group at 10-min intervals up to 50 min and in the total count. Decreased serum triglyceride was observed in both sexes in the 250 mg/kg/day dose groups, which correlated with histopathological findings in the liver. Histopathological evaluation revealed microvesicular vacuolation of hepatocytes in the centrilobular zone of the liver among high-dose group males and cystic follicles in the ovaries of high-dose group females. Hyaline droplets in the epithelial cells of proximal tubules were observed in the kidney of males of the mid- and high-dose group. These kidney changes in males were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This alteration is not considered a hazard to human health (Lehman-McKeeman, 1992; Lehman-McKeeman, 1990). The NOAEL for the repeated dose toxicity endpoint was considered to be 50 mg/kg/day, based on decreased body weight and alterations in the livers and ovaries among animals of the high-dose group (RIFM, 2015e).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 50/3 or 16.7 mg/kg/day.

Therefore, the 3-methyl-5-phenylpent-2-enenitrile MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3-methyl-5-phenylpent-2-enenitrile NOAEL in mg/kg/day by the total systemic exposure to 3-methyl-5-phenylpent-2-enenitrile, 16.7/0.0013, or 12846.

In addition, when correcting for skin absorption (see Section V), the total systemic exposure to 3-methyl-5-phenylpent-2-enenitrile (1.3 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.

11.1.2.2. Derivation of reference dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.167 mg/kg/day.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for 3-methyl-5-phenylpent-2-enenitrile was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 16.7 mg/kg/day by the uncertainty factor, 100 = 0.167 mg/kg/day.

*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: 06/03/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 3-methyl-5-phenylpent-2-enenitrile or any read-across materials. The total systemic exposure to 3-methyl-5-phenylpent-2-enenitrile is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on 3-methyl-5-phenylpent-2-enenitrile or on any read-across materials that can be used to support the reproductive toxicity endpoint. When correcting for skin absorption (see Section V), the total systemic exposure to 3-methyl-5-phenylpent-2-enenitrile (1.3 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: RIFM, 2015e.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.4. Skin sensitization

Based on the existing data on the target material and data on additional materials (Z)-3-methyl-5-phenylpent-2-enenitrile (CAS # 53243-59-7) and (E)-3-methyl-5-phenylpent-2-enenitrile (CAS # 53243-60-0), 3-methyl-5-phenylpent-2-enenitrile is considered a skin sensitizer with a defined NESIL of 270 μg/cm^2.

Table 1
Data summary for 3-methyl-5-phenylpent-2-enenitrile.

LLNA Weighted Mean EC3 Value [No. Studies] μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL
192 [1]	Strong	275	NA	NA	270

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

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

[b] Data derived from CNIH or HMT.

11.1.4.1. Risk assessment. The chemical structure of target material 3-methyl-5-phenylpent-2-enenitrile indicates that it would not be expected to react with skin proteins (Roberts, 2007; OECD Toolbox v4.2). 3-methyl-5-phenylpent-2-enenitrile was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens assay, and positive in an *in vitro* human cell line activation test (h-CLAT) (RIFM, 2016c; RIFM, 2016d; RIFM, 2017). In a murine local lymph node assay (LLNA), 3-methyl-5-phenylpent-2-enenitrile was found to be sensitizing with an EC3 value of 0.77% (192 μg/cm^2) (RIFM, 2007a). In a guinea pig sensitization study, 3-methyl-5-phenylpent-2-enenitrile was not found to be sensitizing (RIFM, 1973). Additionally, in 2 Confirmation of No Induction in Humans tests (CNIHs), 0.2 mL of 3-methyl-5-phenylpent-2-enenitrile at 0.05% (27 μg/cm^2; 0.75 × 0.75-inch patch) in 3:1 DEP:EtOH or at 0.5% (275 μg/cm^2; 0.75 × 0.75-inch patch) in 3:1 DEP:EtOH, no reactions indicative of sensitization were observed in any of the 107 and 110 volunteers, respectively (RIFM, 2007c; RIFM, 2008b).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, 3-methyl-5-phenylpent-2-enenitrile is a sensitizer with a WoE NESIL of 270 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.167 mg/kg/day.

Additional References: RIFM, 1973.

Literature Search and Risk Assessment Completed On: 06/17/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, 3-methyl-5-phenylpent-2-enenitrile 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 3-methyl-5-phenylpent-2-enenitrile 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, 2009). Based on the lack of absorbance, 3-methyl-5-phenylpent-2-enenitrile does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3-methyl-5-phenylpent-2-enenitrile is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on 3-methyl-5-phenylpent-2-enenitrile. Based on the Creme RIFM Model, the inhalation exposure is 0.028 mg/day. This exposure is 16.8 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: 06/24/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3-methyl-5-phenylpent-2-enenitrile was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3-methyl-5-phenylpent-2-enenitrile 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) identified 3-methyl-5-phenylpent-2-enenitrile as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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). Data on persistence and bioaccumulation are reported below and summarized in

the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 3-methyl-5-phenylpent-2-enenitrile presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. For CAS # 93892-89-1.

RIFM, 2000: The biodegradability of the test material was determined using the closed bottle test following the Council Directive 92/69/EEC, Method C.4-E Guidelines. The test material at 2.6 mg/L was suspended in a mineral medium, inoculated with activated sludge, and incubated for 28 days. A 38% biodegradation was observed.

11.2.2.1.2. Ecotoxicity. For CAS # 93892-89-1.

RIFM, 2000: A 48-h *Daphnia magna* acute toxicity test was conducted according to the Council Directive 92/69/EEC Part C, Method 2 Guidelines. The EC0 and EC100 after 48 h were 6.6 mg/L and 41.4 mg/L, respectively. The geometric mean of EC0/EC100 was 16.5 mg/L.

RIFM, 2016b: An algae growth inhibition test was conducted according to the OECD 201 method. Under static test conditions, the 72-h EC50s for inhibition of growth rate (ErC50) and yield (EyC50) were 4.68 mg/L and 3.44 mg/L, respectively. All the results are based on nominal test concentration.

RIFM, 2016a: A 96-h fish (Zebrafish) acute toxicity test was conducted according to the OECD 203 method. Under semi-static test conditions, the LC50 after 96 h was 11.1 mg/L, based on nominal concentration.

11.2.2.1.3. Other available data. 3-Methyl-5-phenylpent-2-enenitrile has been registered for REACH with no additional data at this time.

11.2.3. 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 Framework: Salvito, 2002).

Exposure	Europe	North America
Log K_{ow} Used	2.98	2.98
Biodegradation Factor Used	0.1	0.1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volumes of Use for all CAS #s.

The RIFM PNEC is 3.44 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 06/15/21.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	32.4			1000000	0.0324	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.987	0.573	0.362	10000	0.0362	Vinyl/Allyl Nitriles
ECOSAR Acute Endpoints **(Tier 2)** v1.11	8.312	5.355	6.724			Neutral Organics SAR
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	11.1					
Daphnia		16.5				
Algae		3.44		1000	3.44	

- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/23/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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.

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