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Short Review

RIFM fragrance ingredient safety assessment, 1-ethynylcyclohexyl acetate, CAS Registry Number 5240-32-4

A.M. Api[a], F. Belmonte[a], D. Belsito[b], S. Biserta[a], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.A. Cancellieri[a], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], A.D. Fryer[h], S. Gadhia[a], L. Jones[a], K. Joshi[a], A. Lapczynski[a], M. Lavelle[a], D.C. Liebler[i], M. Na[a], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], F. Rodriguez-Ropero[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[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, 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*
[g] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *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*
[j] *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*
[k] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *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*
[m] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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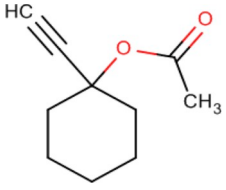

Abbreviation/Definition List:

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, 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
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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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
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
QRA - Quantitative Risk Assessment
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.

1-Ethynylcyclohexyl acetate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1-ethynylcyclohexyl acetate is not genotoxic. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class II material, and the exposure to 1-ethynylcyclohexyl acetate is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the DST for non-reactive materials (900 $\mu g/cm^2$); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 1-ethynylcyclohexyl acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 1-ethynylcyclohexyl acetate 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. (RIFM, 2014a; RIFM, 2015)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a sensitization concern. Exposure is below the DST. (ECHA Dossier: 1-Ethynylcyclohexyl Acetate; ECHA, 2018)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 2.76 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 33.48 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 43.38 mg/L (RIFM Framework; Salvito, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: LC50: 43.38 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.04338 μg/L
Revised PEC/PNECs (2015 IFRA VoU): North America and Europe Not Applicable; Cleared at Screening-level

1. Identification

1. **Chemical Name:** 1-Ethynylcyclohexyl acetate
2. **CAS Registry Number:** 5240-32-4
3. **Synonyms:** 1-Acetoxy-1-ethynylcyclohexane; Cyclohexanol, 1-ethynyl-, acetate; Herbacet #1; 1-Ethynylcyclohexyl acetate
4. **Molecular Formula:** $C_{10}H_{14}O_2$
5. **Molecular Weight:** 166.22
6. **RIFM Number:** 1331
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 215.88 °C (EPI Suite)
2. **Flash Point:** 179.00 °F TCC (81.67 °C)*
3. **Log K_{OW}:** 2.82 (EPI Suite)
4. **Melting Point**: 31.14 °C (EPI Suite)
5. **Water Solubility:** 252.3 mg/L (EPI Suite)
6. **Specific Gravity:** 1.00100 to 1.00900 @ 25.00 °C; 1.00200 to 1.01000 @ 20.00 °C*
7. **Vapor Pressure:** 0.0792 mm Hg @ 20 °C (EPI Suite v4.0), 0.132 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless clear liquid with a medium, natural, acorn, dry, oak, leaves, hay, woody, immortelle, and herbal-like odor

*http://www.thegoodscentscompany.com/data/rw1012811.html, retrieved 06/27/14.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** no reported use in hydroalcoholics (RIFM, 2017)
3. **Inhalation Exposure*:** 0.000017 mg/kg/day or 0.0012 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00025 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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, 2015a, 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 II, moderate (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II	III	I

*See appendix below for explanation.

2. **Analogs** Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
   3. **Read-across Justification:** None

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)

1-Ethynylcyclohexyl acetate is not reported to occur in foods by the VCF*

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Available; accessed 08/29/18.

10. Summary

10.1. Human health endpoint summaries

Based on the current data, 1-ethynylcyclohexyl acetate does not present a concern for genotoxic potential.

10.1.1. Risk assessment

1-Ethynylcyclohexyl acetate was assessed for genotoxic potential in the BlueScreen assay and was found negative for both cytotoxicity and genotoxicity in the presence and absence of metabolic activation (RIFM, 2013).

The mutagenic activity of 1-ethynylcyclohexyl acetate 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2*uvr*A were treated with 1-ethynylcyclohexyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2014a). Under the conditions of the study, 1-ethynylcyclohexyl acetate was not mutagenic in the Ames test.

The clastogenic activity of 1-ethynylcyclohexyl acetate was

Table 1
Maximum acceptable concentrations for 1-ethynylcyclohexyl acetate that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.69%	NRU[b]
2	Products applied to the axillae	0.021%	0.0040
3	Products applied to the face using fingertips	0.41%	NRU[b]
4	Fine fragrance products	0.39%	NRU[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	NRU[b]
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	NRU[b]
8	Products with significant ano-genital exposure	0.041%	No data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0067
10	Household care products with mostly hand contact	2.7%	0.016
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	NRU[b]

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 1-ethynylcyclohexyl acetate in DMSO at concentrations up to 1664 μg/mL. A statistically significant increase in the frequency of binucleated cells with micronuclei (BNMN) was observed at 100 and 200 μg/mL in the approximate 24-h treatment in the absence of S9. Due to the absence of a concentration-related response and observing a significant increase in the BNMN frequency at a concentration producing considerably high cytotoxicity, the 24-h treatment in the absence of S9 was re-evaluated at concentrations ranging from 22.4 to 300 μg/mL. No statistically significant increase in the BNMN frequency was observed at any evaluated concentration in the 3- and approximately 24-h treatment without S9 (RIFM, 2015). Under the conditions of the study, 1-ethynylcyclohexyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 1-ethynylcyclohexyl acetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/08/18.

10.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 1-ethynylcyclohexyl acetate or on any read-across materials. The total systemic exposure to 1-ethynylcyclohexyl acetate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.3. Risk assessment

There are no repeated dose toxicity data on 1-ethynylcyclohexyl acetate or on any read-across materials that can support the repeated dose toxicity endpoint. The total systemic exposure to 1-ethynylcyclohexyl acetate (0.25 μg/kg bw/day) is below the TTC (9 μg/kg bw/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/01/18.

10.1.4. Developmental and reproductive toxicity

There are no developmental and reproductive toxicity data on 1-ethynylcyclohexyl acetate or on any read-across materials. The total systemic exposure to 1-ethynylcyclohexyl acetate is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

10.1.5. Risk assessment

There are no developmental and reproductive toxicity data on 1-ethynylcyclohexyl acetate or on any read-across materials that can be used to support the developmental and reproductive toxicity endpoints. The total systemic exposure to 1-ethynylcyclohexyl acetate (0.25 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/18/18.

10.2. Skin sensitization

Based on the application of the non-reactive DST, 1-ethynylcyclohexyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.3. Risk assessment

The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree 2.6.13). 1-Ethynylcyclohexyl acetate was found to be negative in the *in vitro* direct peptide reactive assay (DPRA) and KeratinoSens tests and positive in a human Cell Line Activation Test (h-CLAT) (https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/22096/7/5/2/?documentUUID=54cf3f4e-6372-4a7b-bd20-07af94edb052, ECHA, 2018, accessed 10/12/18). No predictive tests in animal models exist for this material. In a confirmatory human repeat insult patch test (HRIPT) with 0.2% (110 μg/cm^2) 1-ethynylcyclohexyl acetate in 1:3 ethanol:diethyl phthalate (EtOH:DEP) or 2% in 98% SDA (1550 μg/cm^2), no reactions indicative of sensitization were observed in any of the studies involving 107 and 39 volunteers, respectively (RIFM, 2014b; RIFM, 1971).

Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Roberts, 2015; Safford, 2008, 2011, 2015b). A negative DPRA supports the use of non-reactive DST (https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/22096/7/5/2/?

documentUUID = 54cf3f4e-6372-4a7b-bd20-07af94edb052, ECHA, 2018; accessed 10/12/18). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 1-ethynylcyclohexyl acetate that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/03/19.

Phototoxicity/Photoallergenicity:

Based on the available UV/Vis spectra, 1-ethynylcyclohexyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.3.1. Risk assessment

There are no phototoxicity studies available for 1-ethynylcyclohexyl acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 500 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on lack of absorbance, 1-ethynylcyclohexyl acetate does not present a concern for phototoxicity or photoallergenicity.

10.3.2. UV spectra analysis

The available spectra indicate no significant absorbance in the range of 290–500 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 $L\,mol^{-1} \cdot cm^{-1}$ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/18/18.

10.3.3. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 1-ethynylcyclohexyl acetate is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.3.4. Risk assessment

There are insufficient inhalation data available on 1-ethynylcyclohexyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.0012 mg/day. This exposure is 391.7 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/12/18.

10.4. Environmental endpoint summary

10.4.1. Screening-level assessment

A screening-level risk assessment of 1-ethynylcyclohexyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 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, 1-ethynylcyclohexyl acetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.1 (US EPA, 2012a) did not identify 1-ethynylcyclohexyl acetate as 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 v4.1).

10.4.2. Risk assessment

Based on the current VoU (2015), 1-ethynylcyclohexyl acetate does not present a risk to the aquatic compartment in the screening-level assessment.

10.4.3. Key studies

Biodegradation: No data available.

Ecotoxicity: No data available.

10.4.4. Other available data

1-Ethynylcyclohexyl acetate has been pre-registered for REACH with no additional data at this time.

10.4.5. 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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	43.38			1,000,000	0.04338	

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

Exposure	Europe	North America
Log K_{ow} used	2.82	2.82
Biodegradation Factor Used	0	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQ for this material is < 1. No additional assessment is necessary.

The RIFM PNEC is 0.04338 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the 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: 10/01/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **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/

11.1. 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 01/31/19.

Declaration of interests

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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree.

Q1. Normal constituent of the body? No.

Q2. Contains functional groups associated with enhanced toxicity? No.

Q3. Contains elements other than C, H, O, N, and divalent S? No.

Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.

Q6. Benzene derivative with certain substituents? No.

Q7. Heterocyclic? No.

Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No.

Q17. Readily hydrolyzed to a common terpene? No.

Q19. Open chain? No.

Q23. Aromatic? No.

Q24. Monocarbocyclic with simple substituents? No.

Q18. One of the list (see Cramer et al., 1978 for detailed explanation on list of categories)? Yes. Class moderate (class II).

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