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RIFM fragrance ingredient safety assessment, cyclohexyl acetate, CAS Registry Number 622-45-7

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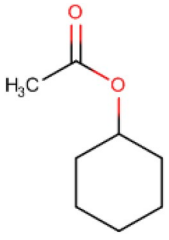

Abbreviation/Definition List:

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

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EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
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 under the limits described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
Cyclohexyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cyclohexyl acetate is not genotoxic. Based on the existing data and the application of DST, cyclohexyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use. Data on read-across alcohol cyclohexanol (CAS # 108-93-0) and read-across acid acetic acid (CAS # 64-19-7) provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to cyclohexyl acetate is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; cyclohexyl acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cyclohexyl 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 expected to genotoxic.	(RIFM, 2017b; RIFM, 2017c)
Repeated Dose Toxicity: NOAEL = 158 mg/kg/day.	(ECHA Dossier: Cyclohexanol; ECHA, 2011)
Reproductive Toxicity: NOAEL = 158 mg/kg/day.	(ECHA Dossier: Cyclohexanol; ECHA, 2011)
Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.	
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: 3.02 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 25.7 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 299.0 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: 299.0 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.2990 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Cyclohexyl acetate
2. **CAS Registry Number:** 622-45-7
3. **Synonyms:** Acetic acid, cyclohexyl ester; Cyclohexane acetate; ｱﾙｶﾝｻﾝ(C = 1 ~ 6)ｼｸﾛﾍｷｼﾙ; 酢酸ｼｸﾛﾍｷｼﾙ; Cyclohexyl acetate
4. **Molecular Formula:** $C_8H_{14}O_2$
5. **Molecular Weight:** 142.2
6. **RIFM Number:** 885
7. **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 174 °C H 750 mm Hg (FMA Database), 61–62 °C (Katz, 1955), 179.41 °C (EPI Suite)
2. **Flash Point:** 58 °C (GHS), 136 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.64 (EPI Suite)
4. **Melting Point**: −26.22 °C (EPI Suite)
5. **Water Solubility:** 453.8 mg/L (EPI Suite)
6. **Specific Gravity:** 0.967 (FMA Database)
7. **Vapor Pressure:** 0.949 mm Hg @ 20 °C (EPI Suite v4.0), 0.9 mm Hg 20 °C (FMA Database), 1.35 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Pale yellow or colorless oily liquid with sweet, fruity, chemical odor

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.013% (RIFM, 2017a)
3. **Inhalation Exposure*:** 0.00064 mg/kg/day or 0.050 mg/day (RIFM, 2017a)
4. **Total Systemic Exposure**:** 0.00098 mg/kg/day (RIFM, 2017a)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Cyclohexanol (CAS # 108-93-0) and acetic acid (CAS # 64-19-7)
   c. **Reproductive Toxicity:** Cyclohexanol (CAS # 108-93-0) and acetic acid (CAS # 64-19-7)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

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

Dwarf quince (*Chaenomeles japonica*)
Grape brandy
Macadamia nut (*Macadamia integrifolia*)
Passion fruit
Sauerkraut
Soybean (*Glycine max. L. merr.*)

*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

Pre-registered on 11/3/2010; no dossier available as of 11/05/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. The mutagenic activity of cyclohexyl 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with cyclohexyl 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, 2017b). Under the conditions of the study, cyclohexyl acetate was not mutagenic in the Ames Test.

The clastogenic activity of cyclohexyl acetate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with cyclohexyl acetate in DMSO at concentrations up to 1420 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. Cyclohexyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels/the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2017c). Under the conditions of the study, cyclohexyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 1/02/18.

10.1.2. Repeated dose toxicity

The MOE for cyclohexyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on cyclohexyl acetate. Cyclohexyl acetate is expected to be hydrolyzed to cyclohexanol (CAS # 108-93-0; see section 5) and acetic acid (CAS # 64-19-7; see section 5). There are sufficient repeated dose toxicity data on cyclohexanol. In an OECD 422 compliant (GLP status not indicated) combined repeated dose/reproductive/developmental toxicity screening test, Sprague Dawley rats (15/sex/concentration) were treated with cyclohexanol vapors via whole-body inhalation at 0, 50, 150, and 450 ppm (equivalent to 0, 0.21, 0.61, and 1.84 mg/L/day). Animals were exposed for 6 h/day, 5 days/week, for 13 weeks (females) or 16 weeks (males). The only modifications to the original OECD 422 were an extension of the exposure period, a 4-week recovery period for 5 males/group, and sperm motility and concentration measurements. The high dose, 450 ppm, was reduced to 400 ppm (equivalent to approximately 1.64 mg/L/day) after 10 weeks of exposure due to mortality of 3 males on days 37, 38, and 60 and 1 female (euthanized in extremis) on day 17. Microscopically, the cause of these deaths could not be determined. However, because these deaths occurred at the highest concentration level, they were considered treatment-related. Decreased activity and prostration were reported among animals of the high-dose group immediately following exposure. No other treatment-related effects were reported for parameters observed such as ophthalmoscopic evaluations, functional observational battery, motor activity, bodyweight gain, food consumption, hematology, clinical biochemistry, urinalysis, organ weights, or macroscopic and microscopic evaluations. The NOAEC was considered to be 0.61 mg/L/day (equivalent to NOAEL of 158.18 mg/kg/day using standard minute volume and body weight parameters for Sprague Dawley rats) based on the mortality among high-dose animals (ECHA, 2011).

Based on the available data on acetic acid (EFSA, 2012; US FDA, 2018), acetic acid does not show specific reproductive or developmental toxicity. As such, acetic acid does not pose any systemic (repeated dose), developmental, or reproductive toxicity to human health when used in fragrances.

The NOAEL of 158 mg/kg/day for cyclohexanol was considered for the safety assessment on cyclohexyl acetate. Therefore, the cyclohexyl acetate MOE can be calculated by dividing the cyclohexanol NOAEL in mg/kg/day by the total systemic exposure to cyclohexyl acetate, 158/0.00098 or 161224.

In addition, the total systemic exposure to cyclohexyl acetate (0.98 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Wakabayashi et al., 1991; Perbellini et al., 1981; Treon et al., 1943.

Literature Search and Risk Assessment Completed On: 01/09/2018.

10.1.3. Reproductive toxicity

The MOE for cyclohexyl acetate is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on cyclohexyl acetate. Cyclohexyl acetate is expected to be hydrolyzed to cyclohexanol (CAS # 108-93-0; see section 5) and acetic acid (CAS # 64-19-7; see section 5).

An OECD 422–compliant (GLP status not indicated) combined repeated dose/reproductive/developmental toxicity screening test, Sprague Dawley rats (15/sex/concentration) were treated with cyclohexanol vapors via whole-body inhalation at 0, 50, 150, and 450 ppm (equivalent to 0, 0.21, 0.61, and 1.84 mg/L/day). Animals were exposed for 6 h/day, 5 days/week, for 13 weeks (females) or 16 weeks (males). The only modifications to the original OECD 422 were an extension of the exposure period, a 4-week recovery period for 5 males/group, and sperm motility and concentration measurements. The high dose (450 ppm) was reduced to 400 ppm (equivalent to approximately 1.64 mg/L/day) after 10 weeks of exposure due to mortality of 3 males on days 37, 38, and 60, and 1 female (euthanized in extremis) on day 17. Microscopically, the cause of these deaths could not be determined. However, because these deaths occurred at the highest concentration level, they were considered treatment-related. Decreased activity and prostration were reported among animals of the high-dose group immediately following exposure. In the high-dose group, 2/11 pregnancies (18.2%) resulted in no viable pups at parturition and lower mean pup weights (10%–12%) at birth and postnatal day 4. No treatment-related adverse effects were reported in histological examination. High-dose males showed a reduction in testicular sperm counts, but they were within historical data range, and recovery groups had sperm counts comparable to controls; hence this effect was not considered as an adverse effect. The NOAEC for reproductive and development toxicity was considered to be 150 ppm (0.61 mg/L), based on treatment-related effects observed among high-dose animals (450/400 ppm) with few pregnancies along with no viable fetuses and reduced pup weights (ECHA, REACH Dossier: Cyclohexanol).

In another study, male rabbits (5/sex/group, weighing 1.5–2 kg), were treated orally with cyclohexanol (diluted with olive oil) at 25 mg/kg/day (groups 2 and 3) for a period of 40 days. Group 1 animals received vehicle alone and served as controls. Group 2 was allowed to recover for a period of 70 days following cessation of cyclohexanol administration. Microscopically, testes showed degenerative changes with loss of type A spermatogonia, spermatocytes, spermatids, and spermatozoa. Spermatids showed morphological changes; cytolysis and chromatolysis were common. Leydig cells were shrunken with scant cytoplasm and nuclei reduced in diameter. Reduced luminal epithelium and scanty stereocilia were reported in histopathology of epididymides. The lumen of the cauda epididymides and ductus deferens were devoid of spermatozoa. Degenerating cells were reported in few tubules. Reversibility was observed for effects observed on testes and epididymides. After the recovery period, no treatment-related effects were reported for spermatogenesis, organ weights, seminiferous tubule, and Leydig cells nuclear dimensions. Histopathology of the liver did not show any effect except for the degranulation of the hepatoplasm. A statistically significant reduction was reported for RNA, protein, sialic acid, and glycogen in testes and epididymides in treated animals. The testicular cholesterol increased significantly whereas acid phosphatase enzyme activity was reduced. Adrenal ascorbic acid values were also decreased. All these changes were reversed to subnormal values after 70 days of recovery. A statistically significant reduction in serum protein contents and an elevation of serum cholesterol, phospholipids, triglycerides, bilirubin, pyruvate transaminase, and alkaline phosphatase was reported. No treatment-related effects were reported for blood sugar and blood urea. Serum transaminase, triglycerides, and protein levels showed reversibility after 70 days of recovery whereas total cholesterol, phospholipids, bilirubin, and phosphatase enzyme activity remained unaltered as compared to the treatment group. Hematological parameters were in the normal range. Therefore, cyclohexanol at the dose of 25 mg/kg/day (daily, for 40 days) produced a brief period of infertility by inhibiting the process of spermatogenesis at the spermatocyte and spermatid levels, which recovered after 70 days of recovery. However, limited details were given in the study report. Data on the test compound (purity), dosing method (means of oral administration), and in-life parameters (body weight, clinical signs) were not mentioned (Dixit et al., 1980).

Since the OECD 422 study (a longer duration study, approximately 16 weeks) on rats did not show alteration in male fertility at doses tested higher than the study performed on male rabbits (approximately 6 weeks), the study on rabbits was not considered towards the safety

Table 1
Maximum acceptable concentrations for cyclohexyl 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 Concentration in Finished Products
1	Products applied to the lips	0.07%	0.00%
2	Products applied to the axillae	0.02%	0.00%[b]
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.00%[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.01%
6	Products with oral and lip exposure	0.23%	0.00%[b]
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.02%
10	Household care products with mostly hand contact	2.70%	0.03%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	1.40%

Note:
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

assessment. Therefore, the NOAEL for reproductive toxicity was considered to be 158 mg/kg/day.

Based on the available data on acetic acid (EFSA, 2012; US FDA, 2018), acetic acid does not show specific reproductive or developmental toxicity. As such, acetic acid does not pose any systemic (repeated dose), developmental, or reproductive toxicity to human health when used in fragrances.

Therefore, the cyclohexyl acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the cyclohexanol NOAEL in mg/kg/day by the total systemic exposure to cyclohexyl acetate, 158/0.00098 or 161224.

In addition, the total systemic exposure to cyclohexyl acetate (0.98 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/09/2018.

10.1.4. Skin sensitization

Based on the existing data and the application of DST, cyclohexyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v4.1). No predictive skin sensitization studies are available for cyclohexyl acetate or read-across materials. In 2 human maximization tests, no skin sensitization reactions were observed (RIFM, 1977; RIFM, 1974).

Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Safford et al., 2015b; Roberts et al., 2015). 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 cyclohexyl acetate that present no appreciable risk for skin sensitization based on the non-reactive DST. These concentrations are not limits; they represent maximum acceptable concentrations based on the DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/21/17.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for cyclohexyl acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, cyclohexyl acetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant 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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/11/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for material cyclohexyl acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are insufficient inhalation data available on cyclohexyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.050 mg/day. This exposure is 28.0 times lower than the Cramer Class I TTC value of 1.4 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: Carpenter et al., 1974; Frantik et al., 1994.

Literature Search and Risk Assessment Completed On: 01/08/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of cyclohexyl 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	299.0			1,000,000	0.2990	

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, cyclohexyl 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 v4.11 (US EPA, 2012a) did not identify cyclohexyl acetate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (EFSA, 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.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), cyclohexyl acetate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.3.3. Other available data. Cyclohexyl acetate 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.

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.64	2.64
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 additional assessment is necessary.

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

The RIFM PNEC is 0.2990 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: 12/19/17.

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/

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 10/09/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.010.

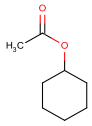
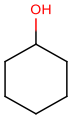
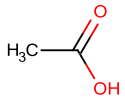
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	Cyclohexyl acetate	Cyclohexanol	Acetic acid
CAS No.	622-45-7	108-93-0	64-19-7
Structure			
Similarity (Tanimoto Score)		NA	NA
Read-across Endpoint		• Repeated dose toxicity • Reproductive toxicity	• Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_8H_{14}O_2$	$C_6H_{12}O_1$	$C_2H_4O_2$
Molecular Weight	142.20	100.16	60.05
Melting Point (°C, EPI Suite)	−26.22	−33.40	−21.26
Boiling Point (°C, EPI Suite)	179.41	161.73	122.30
Vapor Pressure (Pa @ 25 °C, EPI Suite)	180	86.6	$2.29^{E}+003$
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.64	1.23	−0.17
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	453.8	42000	1000000
J_{max} (mg/cm^2/h, SAM)	123.658	953.294	6283.044
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.23E+001	4.96E-001	5.55E-002
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	• Carboxylic acids (Hepatotoxicity alert)
Reproductive and Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, without OH or NH2	• Weak binder, OH group	• Non-binder, Non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Toxicant (good reliability)	• Toxicant (low reliability)
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	No metabolites

Summary

There are insufficient toxicity data on cyclohexyl acetate (CAS # 622-45-7). Hence, *in silico* evaluation was conducted to determine read-across

analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, cyclohexanol (CAS # 108-93-0) and acetic acid (CAS # 64-19-7) were identified as read-across materials with sufficient data for toxicological evaluation.

13. Conclusions

- Read-across alcohol cyclohexanol (CAS # 108-93-0) and read-across acid acetic acid (CAS # 64-19-7) were used as read-across analogs for the target ester cyclohexyl acetate (CAS # 622-45-7) for the repeated dose and reproductive toxicity endpoints.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites of the target.
  - o Structural differences between the target substance and the read-across analog are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o The target substance and the read-across analogs have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v3.4, structural alerts for the endpoints evaluated are consistent between the target substance and the read-across analog.
  - o The read-across acid is given an alert of HESS categorization for repeated dose and developmental toxicity by CAESAR. According to the Human Metabolome Database, acetic acid is one of the common constituents of the human body. These small acids are excreted via different routes very easily. The data shows that acetic acid at current levels of exposure does not pose a concern for human health or environmental endpoints. Therefore, the alert will be superseded by data.
  - o The read-across analogs are predicted to be toxicants by the CAESAR model for developmental toxicity. The target substance does not have any alert. This alert for read-across analog is possibly due to the fact that it is a branched acid. According to the data described in the reproductive toxicity section above, acetic acid does not contribute to the reproductive and developmental toxicity. Therefore, the alert will be superseded by data.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target substance.

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