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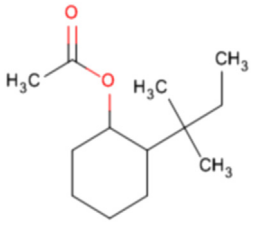
Short review

RIFM fragrance ingredient safety assessment, Amylcyclohexyl acetate (mixed isomers), CAS Registry Number 67874-72-0

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

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677 USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany*
[f] *Member RIFM Expert Panel, 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 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), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan*

Version: 090717. This version replaces any previous versions.
Name: Amylcyclohexyl acetate (mixed isomers)
CAS Registry Number: 67874-72-0



Abbreviation/Definition List:

2-Box Model- a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF- Assessment Factor

BCF- Bioconcentration Factor

Creme RIFM model- The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach

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

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DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA- European Chemicals Agency
EU- Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD- Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA- North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
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
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- Ultra Violet/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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
The material (amylcyclohexyl acetate (mixed isomers)) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that amylcyclohexyl acetate (mixed isomers) is not genotoxic. Data from the amylcyclohexyl acetate (mixed isomers) and read-across analog 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) show that amylcyclohexyl acetate (mixed isomers) is not a concern for skin sensitization. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose, developmental and reproductive toxicity endpoints were completed using 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) and *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5) as read-across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, amylcyclohexyl acetate (mixed isomers) 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, 2009b; RIFM, 2009a)
Repeated Dose Toxicity: NOAEL = 17 mg/kg/day. (JECDB, 2013)
Developmental and Reproductive Toxicity: NOAEL = 150 mg/kg/day and 500 mg/kg/day respectively. (JECDB, 2013)
Skin Sensitization: Not sensitizing. (RIFM, 2002)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 17.1% (OECD 310) (RIFM, 2012a)

Bioaccumulation: Critical Measured Value: Moderate metabolized (Fish S9 Liver Fractions) (RIFM, 2010)

Ecotoxicity: Critical Ecotoxicity Endpoint: 7-day Fish (Fathead Minnow) NOEC: 0.9 mg/l (RIFM, 2005)

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: 7-day Fish (Fathead Minnow) NOEC: 0.9 mg/l (RIFM, 2005)

RIFM PNEC is: 18 μg/l

- Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe < 1

1. Identification

1. **Chemical Name:** Amylcyclohexyl acetate (mixed isomers)
2. **CAS Registry Number:** 67874-72-0
3. **Synonyms:** 2-*t*-Amylcyclohexyl acetate; Amylcyclohexyl acetate (mixed isomers); Cyclohexanol, 2-(1,1-dimethylpropyl)-, acetate; 2-*tert*-Pentylcyclohexyl acetate; 脂肪酸(C = 2～4)アルキル(C = 1～5)シクロヘキシル; 2-(1,1-Dimethylpropyl)cyclohexyl acetate; Coniferan; Cypressan; Amyl cyclohexyl acetate
4. **Molecular Formula:** $C_{13}H_{24}O_2$
5. **Molecular Weight:** 212.33
6. **RIFM Number:** 570

2. Physical data

1. **Boiling Point:** 250.47 °C [US EPA, 2012a]
2. **Flash Point:** > 200 °F; CC [FMA]
3. **Log K_{ow}:** 4.91 [US EPA, 2012a]
4. **Melting Point:** 21.79 °C [US EPA, 2012a]
5. **Water Solubility:** 2.404 mg/L [US EPA, 2012a]
6. **Specific Gravity:** 0.93900 to 0.94700 @ 25.00 °C*
7. **Vapor Pressure:** 0.0168 mm Hg @ 20 °C [US EPA, 2012a], 0.0266 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless liquid with a balsamic-green and somewhat sweet odor.

*http://www.thegoodscentscompany.com/data/rw1009711.html#tophyp, retrieved 6/9/2015.

3. Exposure

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.13% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00066 mg/kg/day or 0.047 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0053 mg/kg/day (RIFM, 2016)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class 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:** 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5); *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5)
   c. **Developmental and Reproductive Toxicity:** 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5); *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5)
   d. **Skin Sensitization:** 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5)
   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)

Amylcyclohexyl acetate (mixed isomers) has not been 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 that contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH Dossier

Pre-registered for 11/30/2010; no dossier available as of 8/30/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, amylcyclohexyl acetate (mixed isomers) does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of amylcyclohexyl acetate (mixed isomers) was assessed in an Ames 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 and TA1537 and *Escherichia coli* strain WP2uvrA were treated with amylcyclohexyl acetate (mixed isomers) in DMSO (dimethyl sulfoxide) at concentrations ranging from 5 to 5000 μg/plate in the presence and absence of metabolic activation (S9 mix). No significant increase in the number of revertant colonies was observed (RIFM, 2009b). Under the conditions of the study, amylcyclohexyl acetate (mixed isomers) was considered not mutagenic in the Ames test.

The clastogenic potential of amylcyclohexyl acetate (mixed isomers) was assessed in an *in vitro* chromosomal aberration assay conducted in compliance with GLP regulation and in accordance with OECD TG 473. Cultured Chinese Hamster Ovary (CHO) cells were treated with amyl cyclohexyl acetate (mixed isomers) in DMSO at concentrations 10, 20, 30, 35, 40 and 45 μg/mL without metabolic activation and 25, 50, 60, 70, 80 and 90 μg/mL with metabolic activation. Amylcyclohexyl acetate (mixed isomers), did not induce a statistically significant increase in the percentage of cells with aberrations both with and without metabolic activation compared to the solvent controls, at the concentrations tested (RIFM, 2009a). Under the conditions of the study, amylcyclohexyl acetate (mixed isomers) does not exhibit clastogenic potential.

Based on the available data, amylcyclohexyl acetate (mixed isomers) does not present a concern for genotoxic potential.

Additional References: RIFM, 2009c.

Literature Search and Risk Assessment Completed On: 06/06/14.

10.1.2. Repeated dose toxicity

The margin of exposure for amylcyclohexyl acetate (mixed isomers) 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 amylcyclohexyl acetate (mixed isomers). Read-across materials, *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5; see Section 5) and 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5; see Section 5) have sufficient repeated dose toxicity data. An OECD/GLP 422 dietary combined oral repeated dose toxicity study and reproduction/developmental toxicity screening test was conducted in Wistar rats. The test material, *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5), was administered to groups of 12 rats/sex/dose, selected to achieve dose levels of 0, 75, 200 and 500 mg/kg/day. The measured intake was 0, 56, 168 and 505 mg/kg/day in males and 0, 52, 151 and 437 mg/kg/day in females. Lower body weight and body weight gain were reported among high dose males, during the first week of the study. Decreased body weight gains in the mid and high dose females were also reported during the first week of dosing. This was considered to be due to the palatability of the test material and not considered to be of toxicological relevance. Food consumption was lower among females of the mid and high dose groups during the first week of dosing. No other treatment-related mortalities were reported. At necropsy, a dose related statistically significant increase in the relative kidney weights was observed among males in the mid and high dose groups. No effects on organ weights were observed in female animals. A significant increase in the relative liver weight (15% increase as compared to control) was observed among high dose males. Since no related effects were observed during histopathology of the liver and on clinical chemistry parameters, these alterations were considered to be non-adverse (Hall et al., 2012). Microscopic examination revealed α2μ-microglobulin nephropathy among treated males only. This observed effect in rats is consistent with well-documented changes that are peculiar to the male rat in response to treatment with some hydrocarbons. This effect is, therefore, not indicative of a hazard to human health (Lehman-McKeeman and Caudill, 1992 and Lehman-McKeeman et al., 1990). Thus, the NOAEL for repeated dose toxicity was considered to be 500 mg/kg/day, the highest dose tested (equivalent to 505 and 437 mg/kg/day in males and females, respectively). In another study, the test material, 2-*tert*-butylcyclohexan-1-yl acetate (CAS # 88-41-5; see Section 5), was administered via gavage at doses of 0 (corn oil), 50, 150 or 500 mg/kg/day to groups of 12 SD rats/sex/dose group. Additional non-mating groups of 10 female rats/dose were administered corn oil vehicle or 500 mg/kg/day of test material during the entire length of the treatment period. 5 rats/sex from the mating group and 5 female rats from the non-mating group were maintained treatment-free for 14 days following the last administered dose. Mortality was reported among high dose females (total of 7). Alterations in clinical observations included clonic convulsions among surviving animals of the high dose group. However, these symptoms were not observed among recovery group animals thus, suggesting recovery. Body weight and body weight gains among high dose males were reduced along with reduced food consumption among high dose animals, both of which showed complete recovery among recovery group animals. RBC counts among high dose females were reduced and the reasons remained unknown. There was a statistically significant increase in the relative kidney weights among treated males and a statistically significant increase in the absolute kidney weights among high dose males. The kidneys among males of the mid and high dose groups were enlarged. Microscopic examination of the kidneys revealed α2μ-globulin related alterations among males only. These are species specific effects and not a concern for human health (Lehman-McKeeman and Caudill, 1992 and Lehman-McKeeman et al., 1990). Non-adverse alterations in the liver included an increase in the absolute and relative liver weights among treated males (up to 20% increase). There was an increase in the relative liver weights among mid and high dose group females (up to 17%). The absolute liver weight among high dose females was also increased. There was an increase in the absolute and relative liver weight among non-mated females as well. Alterations in the liver were not accompanied by related changes in clinical chemistry and necrosis was not observed during microscopic

evaluation. Hence these alterations were not considered to be adverse. Secondary alterations in the thyroid (thyroid weight increase and thyroid cellular hypertrophy) were considered to be secondary to the related alteration in the liver and hence were not considered to be of adverse nature. The absolute and relative adrenal weights were increased among treated females of the high dose group. Microscopic examination revealed vacuolization of the epithelial cells among these high dose treated females. The reasons for alterations in adrenals among females remained unknown. There was an increase in the absolute and relative thymus weights among the high dose treated females. Recovery group females were also reported to have an increase in thymus weight, suggesting a test material related non-reversible effect. Thus, the NOAEL for the repeated dose toxicity was considered to be 50 mg/kg/day, based on incidences of mortality (high dose), convulsions (high dose), decreased RBC counts (high dose) alteration in adrenals (mid and high dose) and thymus (high dose) among females. The most conservative NOAEL of 50 mg/kg/day was selected for the repeated dose toxicity endpoint.

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

Thus, the derived NOAEL for the repeated dose toxicity data is 50/3 or 17 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.

Therefore, the amylcyclohexyl acetate (mixed isomers) MOE is equal to the 2-*tert*-butylcyclohexan-1-yl acetate NOAEL in mg/kg/day divided by the total systemic exposure to amylcyclohexyl acetate (mixed isomers), 17/0.0098 or 1735.

In addition, the total systemic exposure to amylcyclohexyl acetate (mixed isomers) (9.8 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for a Cramer Class I material for the repeated dose toxicity endpoint at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/04/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for amylcyclohexyl acetate (mixed isomers) is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on amylcyclohexyl acetate (mixed isomers). Read-across materials, *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5; see Section 5) and 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5; see Section 5), have sufficient developmental toxicity data. An OECD/GLP 422 dietary combined oral repeated dose toxicity study and reproduction/developmental toxicity screening test was conducted in Wistar rats. The test material, *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5), was administered to groups of 12 rats/sex/dose, selected to achieve dose levels of 0, 75, 200 and 500 mg/kg/day. The measured intake was 0, 56, 168 and 505 mg/kg/day in males and 0, 52, 151 and 437 mg/kg/day in females. There were no treatment-related effects on litter size, pup survival, and pup body weights. Thus, the NOAEL for the developmental toxicity was considered to be 505 mg/kg/day, the highest dose tested among males (RIFM, 2012b). In another combined developmental/reproductive and repeated dose toxicity screening study, test material, 2-*tert*-butylcyclohexan-1-yl acetate (CAS # 88-41-5), was administered via gavage at doses of 0 (corn oil), 50, 150 or 500 mg/kg/day to groups of 12 SD rats/sex/dose group. Additional non-mating groups of 10 female rats/dose were administered corn oil vehicle or 500 mg/kg/day of test material during the entire length of the treatment period. Five rats/sex from the mating group and 5 females from the non-mating group were maintained treatment-free for 14 days following the last administered dose. There were no effects of test material administration on developmental parameters evaluated. The only reported effects on the pups were decreases in body weights and body weight gains (up to 17% decrease) among the highest dose groups from post-natal days 0–4. Thus, the NOAEL for developmental toxicity was considered to be 150 mg/kg/day, based on reduced body weights and body weight gains among pups of the highest dose group (JECDB, 2013). The most conservative NOAEL of 150 mg/kg/day was considered for the developmental toxicity endpoint. **Therefore, the amylcyclohexyl acetate (mixed isomers) MOE is equal to the 2-*tert*-butylcyclohexyl acetate NOAEL in mg/kg/day divided by the total systemic exposure to amylcyclohexyl acetate(mixed isomers), 150/0.0098 or 15306.**

There are no reproductive toxicity data on amylcyclohexyl acetate (mixed isomers). Read-across materials, *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5; see Section 5) and 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5; see Section 5), have sufficient reproductive toxicity data. An OECD/GLP 422 dietary combined oral repeated dose toxicity study and reproduction/developmental toxicity screening test was conducted in Wistar rats. The test material, *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5), was administered to groups of 12 rats/sex/dose, selected to achieve dose levels of 0, 75, 200 and 500 mg/kg/day. The measured intake was 0, 56, 168 and 505 mg/kg/day in males and 0, 52, 151 and 437 mg/kg/day in females. No statistically significant effects were reported on sperm motility parameters, sperm count, sperm morphology and testicular sperm count. The male and female reproductive organs remained unaffected by treatment with test material as evidenced by the lack of histopathological alterations among treated animals. Thus, the reproductive toxicity NOAEL was considered to be 505 mg/kg/day for males and 437 mg/kg/day for females, the highest dose tested (RIFM, 2012b). In another combined developmental/reproductive and repeated dose toxicity screening study, test material, 2-*tert*-butylcyclohexan-1-yl acetate (CAS # 88-41-5), was administered via gavage at doses of 0 (corn oil), 50, 150 or 500 mg/kg/day to groups of 12 SD rats/sex/dose group. Additional non-mating groups of 10 female rats/dose were administered corn oil vehicle or 500 mg/kg/day of test material during the entire length of the treatment period. Five rats/sex from the mating group and 5 females from the non-mating group were maintained treatment-free for 14 days following the last administered dose. There were no effects of test material administration on the reproductive (copulation ability, fertilization ability, fertility and reproductive functions) parameters evaluated. Thus, the NOAEL for reproductive toxicity was considered to be 500 mg/kg/day, the highest dose tested among males (JECDB, 2013). A NOAEL of 500 mg/kg/day, the highest dose tested derived from the gavage study on 2-*tert*-butylcyclohexan-1-yl acetate (CAS # 88-41-5) was considered for the reproductive toxicity endpoint. **Therefore, the amylcyclohexyl acetate (mixed isomers) MOE is equal to the 2-*tert*-butylcyclohexan-1-yl acetate NOAEL in mg/kg/day divided by the total systemic exposure for amylcyclohexyl acetate (mixed isomers), 500/0.0098 or 51020.**

In addition, the total systemic exposure to amylcyclohexyl acetate (mixed isomers) (9.8 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for a Cramer Class I material for the developmental and reproductive toxicity endpoints at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 2/4/2017.

10.1.4. Skin sensitization

Based on existing material specific data and read-across to 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5); amylcyclohexyl acetate (mixed isomers) does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on existing material specific data and read-across material 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5; see Section 5); amylcyclohexyl acetate (mixed isomers) does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig sensitization study, no reactions were reported for 2-*tert*-butylcyclohexyl acetate (RIFM, 1972). Additionally, no reactions indicative of skin sensitization were observed in the human studies to amylcyclohexyl acetate (mixed isomers) or 2-*tert*-butylcyclohexyl acetate (RIFM, 1976; RIFM, 1964a; RIFM, 1975; RIFM, 2002; RIFM, 1964b).

Additional References: None.

Literature Search and Risk Assessment Completed On: 1/25/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectrum, amylcyclohexyl acetate (mixed isomers) does not present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for amylcyclohexyl acetate (mixed isomers) in experimental models. The available UV absorption spectrum indicates no absorption between 290 and 400 nm. The quality of the spectrum does not allow for calculation of molar absorption coefficient. Based on lack of absorbance, amylcyclohexyl acetate (mixed isomers) does not present a concern for phototoxicity or photoallergenicity (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/10/17.

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on amylcyclohexyl acetate (mixed isomers). Based on the Creme RIFM model, the inhalation exposure is 0.047 mg/day. This exposure is 29.8 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: None.

Literature Search and Risk Assessment Completed On: 02/8/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of amylcyclohexyl acetate (mixed isomers) was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates; US EPA, 2012b) is used, and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, amylcyclohexyl acetate (mixed isomers) 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 amylcyclohexyl acetate (mixed isomers) as possibly persistent but not bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental safety assessment section prior to Section 1.

10.2.2. Risk assessment

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

10.2.3. Key studies

10.2.3.1. Biodegradation. **RIFM, 2008**: The biodegradability of the test material was evaluated in the Headspace Test according to the OECD 310 method. No biodegradation was observed after 28 days.

RIFM, 2012a: A two parts enhanced biodegradation test was conducted according to the OECD 310 method. The average cumulative percent biodegradation of the test material at the end of the 28-day initial test was 12.4%. For the second part, the inoculated test medium from the first test was used and study time was extended to 60 days. The average cumulative percent biodegradation of the test material at the end of the 60-day second test was 17.1%.

RIFM, 2010: The *in vitro* stability of the test material was determined in fish S9 liver fractions. Metabolic stability was determined by monitoring the disappearance (GC-MS) of amylcyclohexyl acetate as a function of incubation time (0, 2, 4, 6, 8, and 10 min). The test material was categorized as moderate metabolized.

10.2.3.2. Ecotoxicity. **RIFM, 2005**: Short-term chronic static renewal effluent toxicity tests with *Daphnia magna* were conducted according to EPA/600/4-90/027 and ASTM E729 methods. At the end of 10 day exposure period, the NOEC for survival and reproduction was 7.21 mg/l.

RIFM, 2005: Short-term chronic static renewal effluent toxicity tests with immature fathead minnows, *Pimephales promelas*, were conducted according to EPA/600/4-90/027 and ASTM E729. The 7-day NOEC of amylcyclohexyl acetate in immature fathead minnows (*Pimephales promelas*) was 0.9 mg/l and 3.61 mg/l for growth and survival, respectively.

10.2.3.3. Other available data. Amylcyclohexyl acetate (mixed isomers) has been pre-registered for REACH with no additional data at this time.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	0.859 mg/L			1,000,000	0.000859 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.564 mg/L	0.859 mg/L	0.230 mg/L	10,000	0.023 µg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.422 mg/L	0.313 mg/L	0.710 mg/L			Neutral Organic SAR (Baseline Toxicity)
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish			0.9 mg/L	50	18 µg/L	
Daphnia			7.21 mg/L			
Algae						

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.91	4.91
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 18 µg/l. The revised PEC/PNECs for EU and NA are < 1 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: 03/17/17.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.11.040.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.11.040.

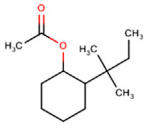
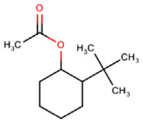
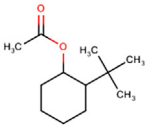
Appendix

Read-across justification

Methods

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

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

	Target material	Read across material	
Principal Name	Amylcyclohexyl acetate (mixed isomers)	2-*tert*-Butylcyclohexyl acetate	*cis*-2-*tert*-Butylcyclohexyl acetate
CAS No.	67874-72-0	88-41-5	20298-69-5
Structure			
Similarity (Tanimoto score)		0.79	0.79
Read-across endpoint		• Skin sensitization • Repeated dose • Developmental and reproductive	• Repeated dose • Developmental and reproductive
Molecular Formula	$C_{12}H_{24}O_2$	$C_{12}H_{22}O_2$	$C_{12}H_{22}O_2$
Molecular Weight	212.33	198.31	198.31
Melting Point (°C, EPISUITE)	21.79	10.93	10.93
Boiling Point (°C, EPISUITE)	250.47	232.55	232.55
Vapor Pressure (Pa @ 25 °C, EPISUITE)	3.54	7.1	2.41
Log Kow (KOWWIN v1.68 in EPISUITE)	4.91	4.2	4.2
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	2.404	7.462	7.462
J_{max} (mg/cm^2/h, SAM)	8.774	17.080	17.080
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.31E-003	9.90E-004	9.90E-004
Repeated dose toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	• Not categorized
Reproductive and developmental toxicity			
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder without OH and NH_2 group	• Non-binder without OH and NH_2 group	• Non-binder without OH and NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (moderate reliability)	• Toxicant (moderate reliability)	• Toxicant (moderate reliability)
Skin Sensitization			
Protein binding by OASIS v1.4	• No alert found	• No alert found	

Protein binding by OECD	• Acylation	• Acylation	
Protein binding potency	• Not possible to classify	• Not possible to classify	
Protein binding alerts for skin sensitization by OASIS v1.4	• No alert found	• No alert found	
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)	
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See supplemental data 1	See supplemental data 2	See supplemental data 3

Summary

There are insufficient toxicity data on the target material amylcyclohexyl acetate (mixed isomers) (CAS # 67874-72-0). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5) and 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) were identified as read-across materials with data for their respective toxicological endpoints.

Conclusion/Rationale

cis-2-*tert*-Butylcyclohexyl acetate (CAS # 20298-69-5) and 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) could be used as read-across analogs for the target material amylcyclohexyl acetate (mixed isomers) (CAS # 67874-72-0) for the skin sensitization, repeated dose, developmental and reproductive toxicity endpoints.

- ○ The target substance and the read-across analogs are structurally similar and belong to the structural class of aliphatic esters.
- ○ The target substance and the read-across analogs share a branched alkyl substituted cyclohexyl structure.
- ○ The key difference between the target substance and the read-across analogs is that the target substance has an isopentane substituted cyclohexyl substructure while the read-across analogs have a *tert*-butyl substituted cyclohexyl substructure. The differences in structure between the target substance and the read-across analogs do not raise additional structural alerts, so the structural differences are not relevant from a toxicological endpoint perspective.
- ○ Similarity between the target substance and the read across analogs is indicated by the Tanimoto scores in the table above. The Tanimoto score is mainly driven by the ester and cyclohexyl fragment. The differences in the structure which are responsible for a Tanimoto score < 1 are not relevant from a toxicological endpoint perspective.
- ○ The target substance and the read-across analog have similar physical-chemical properties. The J_{max} value for the read-across analogs is higher compared to the target substance which predicts that read across analogs will have higher skin absorption compared to the target substance. Any differences in the physical-chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for the toxicological endpoints.
- ○ Structural alerts for the skin sensitization endpoint are consistent between the target substance and the read-across analog as seen in the table above. According to CAESAR v.2.1.6 model, the target substance, as well as the read-across analog, is predicted to be a sensitizer. OECD QSAR toolbox shows a protein binding alert for the target as well as the read across analog. Other *in silico* models for skin sensitization do not show any alert for the target substance or the read across analog. The data described in the skin sensitization section demonstrates that the read-across analog is not a skin sensitizer and is not a concern for skin sensitization endpoint. Hence, the prediction is superseded by the available data.
- ○ The target substance, as well as the read-analogs, are predicted to be toxicants for the developmental endpoint with moderate reliability only by the CAESAR model v.2.1.6. The data described in the developmental and reproductive toxicity section demonstrates that the read-across material is safe to use at the current level of use for developmental toxicity endpoint, thus superseding the *in silico* predictions.
- ○ The target substance and the read-across analog are expected to be metabolized similarly as shown by the metabolism simulator.
- ○ The structural alerts for the toxicological endpoints are consistent between the metabolites of the read-across analog and the target substance.

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