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Short review

RIFM fragrance ingredient safety assessment, ethyl 2-*tert*-butylcyclohexyl carbonate, CAS Registry Number 67801-64-3

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 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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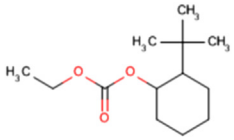

Abbreviation list:

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

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(*continued*)

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.
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
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 reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative 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 (ethyl 2-*tert*-butylcyclohexyl carbonate) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the read across analog 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) show that ethyl 2-*tert*-butylcyclohexyl carbonate is not genotoxic nor does it have skin sensitization potential. 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 and developmental and reproductive toxicity endpoint was 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 along with data on the target material. The environmental endpoints were evaluated, ethyl 2-*tert*-butylcyclohexyl carbonate 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. (JECDB, 2013a: 2-*tert*-butyl-, acetate; RIFM, 2000)
Repeated Dose Toxicity: NOAEL = 17 mg/kg/day. (JECDB, 2013b)
Developmental and Reproductive Toxicity: NOAEL = 150 mg/kg/day and 500 mg/kg/day, respectively. (JECDB, 2013b)
Skin Sensitization: Not sensitizing. (RIFM, 2002)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1976a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening level: 2.4 (Biowin 3) (US EPA, 2012a)
Bioaccumulation: Screening level: 656 l/kg (US EPA, 2012a)
Ecotoxicity: Screening Level: 96-hr Algae EC50: 0.566 mg/l (US EPA, 2012a)
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: 96-hr Algae EC50: 0.566 mg/l (US EPA, 2012a)
RIFM PNEC is: 0.0566 μg/l
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** Ethyl 2-*tert*-butylcyclohexyl carbonate
2. **CAS Registry Number:** 67801-64-3
3. **Synonyms:** 2-*tert*-Butylcyclohexyl ethyl carbonate; Carbonic acid, 2-(1,1-dimethylethyl)cyclohexyl ethyl ester; Ethyl 2-*tert*-butylcyclohexyl carbonate; Floramat; 炭酸=2-*tert*-ブチルシクロヘキシル=エチル
4. **Molecular Formula:** $C_{13}H_{24}O_3$
5. **Molecular Weight:** 228.33
6. **RIFM Number:** 1201

2. Physical data

1. **Boiling Point:** 280.62 °C (US EPA, 2012a)
2. **Flash Point:** 120 °C (RIFM, 1982a)
3. **Log K_{OW}:** 4.4 (RIFM, 2013b), 4.77 (US EPA, 2012a)
4. **Melting Point**: −7.6 °C (US EPA, 2012a)
5. **Water Solubility:** 2.601 mg/l (US EPA, 2012a)
6. **Specific Gravity:** 0.9750 (RIFM, 1982a)
7. **Vapor Pressure:** 0.00337 mm Hg @ 20 °C (US EPA, 2012a), 0.00543 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless liquid with a fruity-woody odor

3. Exposure

1. **Volume of Use (worldwide band):** 10−100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.12% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00058 mg/kg/day or 0.040 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0033 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 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., 2015, 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)

Expert judgment	Toxtree v.2.6	OCED QSAR Toolbox v. 3.2
I*	III	II

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was also determined using expert judgment based on the Cramer decision tree (Cramer et al., 1976). See Appendix below for further details.

2. **Analogs Selected:**
   a. **Genotoxicity:** 2-*tert*-Butylcyclohexyl acetate (CAS # 88-41-5)
   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

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)

Ethyl 2-*tert*-butylcyclohexyl carbonate is not reported to be found in food by the VCF*.

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

8. IFRA standard

None.

9. Reach dossier

Pre-Registered for 2010; No dossier available as of 07/31/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, ethyl 2-*tert*-butylcyclohexyl carbonate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Ethyl 2-*tert*-butylcyclohexyl carbonate

was tested in the BlueScreen assay and was found negative for genotoxicity in the presence and the absence of metabolic activation (RIFM, 2013a). There are no studies assessing the mutagenic activity of ethyl 2-*tert*-butylcyclohexyl carbonate. 2-tert-Butylcyclohexyl acetate (CAS # 88-41-5; see Section 5) was identified as a read across analog. The mutagenic activity of 2-*tert*-butylcyclohexyl acetate was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using both the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA97, TA98, TA100, TA102 and TA1535 were treated with 2-*tert*-butylcyclohexyl acetate in DMSO (dimethyl sulfoxide) at the concentrations up to 5 mg/plate in the presence and absence of metabolic activation. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2000). Under the conditions of the study, 2-*tert*-butylcyclohexyl acetate was considered not mutagenic in the Ames test and this can be extended to ethyl 2-*tert*-butylcyclohexyl carbonate.

There are no studies assessing the clastogenicity of ethyl 2-*tert*-butylcyclohexyl carbonate however, 2-*tert*-butylcyclohexyl acetate was identified as a read across analog. The clastogenic activity of 2-*tert*-butylcyclohexyl acetate was assessed in an *in vitro* chromosome aberration test conducted according to OECD TG 473. The Chinese hamster (CHL/IU) cell line was treated with 2-*tert*-butylcyclohexyl acetate in DMSO for 6-h treatment in the presence of metabolically active microsomal mixture (S9) at the concentrations 27.2, 41.5, 62.2, 93.3 and 140 μg/ml. For the short term and continuous treatments (6, 24 and 48 h) in the absence of S9, the concentrations tested were 20, 40, 60, 80 and 100 μg/ml. There were no significant increases in the number of cells with chromosomal aberrations at the concentrations tested (JECDB, 2013a: 2-*tert*-butyl-, acetate). Under the conditions of the study, 2-*tert*-butylcyclohexyl acetate was considered not clastogenic in the *in vitro* chromosome aberration test and this can be extended to ethyl 2-*tert*-butylcyclohexyl carbonate.

Based on the available data, 2-*tert*-butylcyclohexyl acetate does not present a concern for genotoxic potential and this can be extended to ethyl 2-*tert*-butylcyclohexyl carbonate.

Additional References: None.

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

10.1.2. Repeated dose toxicity

The margin of exposure for ethyl 2-*tert*-butylcyclohexyl carbonate 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 ethyl 2-*tert*-butylcyclohexyl carbonate. 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 increase in the relative kidney weights was observed among males of 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 an increase in the relative kidney weights among treated males and an 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 were seen, including 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. 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 endpoint was considered to be 50 mg/kg/day, the most conservative NOAEL, 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.

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.

Therefore, the ethyl 2-*tert*-butylcyclohexyl carbonate MOE is equal to the 2-*tert*-butylcyclohexan-1-yl acetate NOAEL in mg/kg/day divided by the total systemic exposure to ethyl 2-*tert*-butylcyclohexyl carbonate, 17/0.0033 or 5152.

In addition, the total systemic exposure to ethyl 2-*tert*-butylcyclohexyl carbonate (3.3 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.

* The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

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

10.1.3. Developmental and reproductive toxicity

The margin of exposure for ethyl 2-*tert*-butylcyclohexyl carbonate 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 ethyl 2-*tert*-butylcyclohexyl carbonate. 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, 2012). 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 postnatal 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, 2013b). The most conservative NOAEL of 150 mg/kg/day was considered for the developmental toxicity endpoint. **Therefore, the ethyl 2-*tert*-butylcyclohexyl carbonate MOE is equal to the 2-*tert*-butylcyclohexyl acetate NOAEL in mg/kg/day divided by the total systemic exposure to ethyl 2-*tert*-butylcyclohexyl carbonate, 150/0.0033 or 45455.**

There are no reproductive toxicity data on ethyl 2-*tert*-butylcyclohexyl carbonate. 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, 2012). 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 (JECDB, 2013b). 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 ethyl 2-*tert*-butylcyclohexyl carbonate MOE is equal to the 2-*tert*-butylcyclohexan-1-yl acetate NOAEL in mg/kg/day divided by the total systemic exposure to ethyl 2-*tert*-butylcyclohexyl carbonate, 500/0.0033 or 151515.**

In addition, the total systemic exposure to ethyl 2-*tert*-butylcyclohexyl carbonate (3.3 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007 and 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: 02/02/2017.

10.1.4. Skin sensitization

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

10.1.4.1. Risk assessment. Based on existing material specific data and read across to 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5; see Section 5); ethyl 2-*tert*-butylcyclohexyl carbonate 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 maximization test no sensitization reactions were observed with ethyl 2-*tert*-butylcyclohexyl carbonate (RIFM, 1977). Similarly, in another 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 ethyl 2-*tert*-butylcyclohexyl carbonate or 2-*tert*-butylcyclohexyl acetate (RIFM, 1982b; RIFM, 1976b; RIFM, 2002; RIFM, 1964).

Additional References: None.

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

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available *in vivo* study data, ethyl 2-*tert*-butylcyclohexyl carbonate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 $L \cdot mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). Phototoxic potential of 5% ethyl 2-*tert*-butylcyclohexyl carbonate in olive oil was evaluated in a group of hairless female mice; there were no differences between groups (test material irradiated, test material un-irradiated, and irradiation alone). Based on lack of absorbance and *in vivo* study data, ethyl 2-*tert*-butylcyclohexyl carbonate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/17/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, ethyl 2-*tert*-butylcyclohexyl carbonate, exposure level 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 ethyl 2-*tert*-butylcyclohexyl carbonate. Based on the Creme RIFM model, the inhalation exposure is 0.040 mg/day. This exposure is 35.0 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: RIFM, 1979.

Literature Search and Risk Assessment Completed on: 12/15/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of ethyl 2-*tert*-butylcyclohexyl carbonate 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, which is considered proprietary information, 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, ethyl 2-*tert*-butylcyclohexyl carbonate 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 EPISUITE v4.1 (US EPA, 2012a)identified ethyl 2-*tert*-butylcyclohexyl carbonate 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 EPISUITE v4.1).

10.2.2. Risk assessment

Based on current Volume of Use (2015), ethyl 2-*tert*-butylcyclohexyl carbonate presents 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. Ethyl 2-*tert*-butylcyclohexyl carbonate has been pre-registered for REACH with no additional data at this time.

10.2.4. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/l; PNECs in μg/l).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	2.515 mg/L			1,000,000	0.002515 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.211 mg/L	1.947 mg/L	0.566 mg/L	10,000	0.0566 μg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.311 mg/L	0.929 mg/L	1.731 mg/L			Neutral Organic SAR (Baseline Toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.4	4.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1−10	<1
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 0.0566 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: 3/17.

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

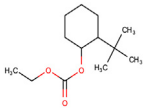
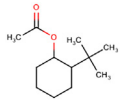
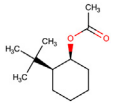
Read across justification

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) and is consistent with the guidance provided by OECD on the reporting of defined approached used within Integrated Approaches for Testing and Assessment or IATA (OECD, 2015) and the European Chemical Agency (ECHA) read across assessment framework or RAAF (ECHA, 2016).

- In essence, materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster was examined. Finally, appropriate read across analogs from the cluster were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints. (Rogers and Hahn, 2010).
- The physicochemical properties of the target substance and the read across analogs were calculated using EPI Suite™ v4.11 developed by US EPA (US EPA, 2012a).
- J_{max} were calculated using RIFM skin absorption model (SAM), and the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6, respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

- The major metabolites for the target and read across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target material	Read across material	
Principal Name	Ethyl 2-*tert*-butylcyclohexyl carbonate	2-*tert*-Butylcyclohexyl acetate	*cis*-2-*tert*-Butylcyclohexyl acetate
CAS No.	67801-64-3	88-41-5	20298-69-5
Structure			
Similarity (Tanimoto score)		0.81	0.89
Read across endpoint		• Genotoxicity • Repeated dose • Developmental and reproductive • Skin sensitization	• Repeated dose • Developmental and reproductive
Molecular Formula	$C_{13}H_{24}O_3$	$C_{12}H_{22}O_2$	$C_{12}H_{22}O_2$
Molecular Weight	228.33	198.31	198.31
Melting Point (°C, EPISUITE)	−7.6	10.93	10.93
Boiling Point (°C, EPISUITE)	73	232.55	232.55
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.724	7.1	2.41
Log Kow (KOWWIN v1.68 in EPISUITE)	4.4[1]	4.2	4.2
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	1.868	7.462	7.462
J_{max} (mg/cm^2/h, SAM)	7.885	17.080	17.080
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	4.65E-003	9.90E-004	9.90E-004
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• AN2 • Schiff base formation • SN1 Nucleophilic attack • SN2, Acylation	
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found	
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found	
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Repeated dose toxicity			
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	• Non toxicant (low 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	• No alert found	• Acylation	
Protein binding potency	• Not possible to classify	• Not possible to classify	
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found	
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (low 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

1. RIFM, 2013b.

Summary

There are insufficient toxicity data on the target material ethyl 2-*tert*-butylcyclohexyl carbonate (CAS # 67801-64-3). Hence, *in silico* evaluation was conducted to determine read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, analogs 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) and *cis*-2-

tert-butylcyclohexyl acetate (CAS # 20298-69-5) were identified as read across materials with data for their respective toxicological endpoints.

- Metabolism of the target substance was not considered for the risk assessment and therefore metabolism data was not reviewed except where it may pertain as described in specific endpoint sections above. Metabolism of the target material ethyl 2-*tert*-butylcyclohexyl carbonate (CAS # 67801-64-3) and both of the read across materials 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) and *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5) were predicted using the rat liver S9 Metabolism Simulator (TIMES SS v.2.27.19) (See table above). The target material as well as the read across analogs are predicted to be metabolized to 2-*tert*-butylcyclohexanol (CAS # 13491-79-7). In addition, the target substance will produce formic acid (CAS # 64-18-6) and methanol (CAS # 67-56-1) as additional metabolic products, while the read across analogs will produce acetic acid (CAS # 64-19-7). The organic acids produced in the metabolism of both of the read across analogs, as well as the target substance are structurally similar. Methanol is the only additional metabolic product produced by the target substance. Methanol does not show any structural alerts towards the genotoxicity, repeated dose, developmental toxicity or skin sensitization endpoint. Hence, 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) and *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5) can be used as read across for the target material ethyl 2-*tert*-butylcyclohexyl carbonate (CAS # 67801-64-3). Both read across analogs were out of domain for *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgement, the model's domain exclusion was overridden and a justification is provided.

Conclusion/Rational

- The following materials were used as read across analogs for the target material ethyl 2-*tert*-butylcyclohexyl carbonate (CAS # 67801-64-3): 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) was used for genotoxicity, reproductive and developmental toxicity and repeated dose toxicity endpoints; *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5) was used for reproductive and developmental toxicity and repeated dose toxicity endpoints; and 4-*tert*-Butylcyclohexyl acetate (CAS # 32210-23-4) was used for the skin sensitization endpoint.
  - The target substance and the read across analogs are structurally similar. The read across analogs belong to the structural class of aliphatic esters with a cyclic alcohol portion while the target belongs to the aliphatic carbonate class, with the same extended fragment on the alcohol portion.
  - The target and analogs are all cyclohexanols with an adjacent *tert*-butyl substituent.
  - The key difference is in the modification of the alcohol. The target is an ethyl carbonate while, the read across analogs are acetate esters. The differences the physicochemical properties show that the read across analogs were absorbed more compared to the target substance, so the bioavailability of the read across analogues will be more than the target substance.
  - Similarity between the target substance and the read across analog is indicated by the Tanimoto scores in the above table. The Tanimoto score is mainly driven by the tert-butylcyclohexyl alcohol portion fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicological endpoint perspective.
  - According to the OASIS model available within OECD QSAR toolbox, 2-*tert*-butylcyclohexyl acetate shows a DNA binding alert which is not seen for the target substance. This is the only *in silico* prediction with a DNA binding alert. All of the other genotoxicity models do not show any alert. The data described in the genotoxicity section above demonstrates that the read across material is not a concern for genotoxicity. Hence, the prediction is superseded by the data.
  - According to the developmental toxicity CAESAR V2.1.6 model, both of the read across analogues are predicted to be toxicants with moderate reliability and the target to be a non-toxicant with low reliability. The data described in developmental and reproductive section demonstrates that the read across material is safe to use within given margin of exposure and level of use for developmental toxicity endpoint, thus superseding the *in silico* predictions.
  - Other structural alerts for reproductive and developmental toxicity and repeated dose toxicity endpoints are consistent between the target substance and the read across analog as seen in the table above.
  - 2-*tert*-Butylcyclohexyl acetate shows protein binding alert by OECD QSAR Toolbox v3.4. This alert is not seen for the target. According to the CAESAR model, the target and the read across analog are predicted with low reliability to be sensitizers. Other protein binding predictions do not show any alert for the read across. The data described in the skin sensitization section demonstrates that the read across materials are not sensitizers, thereby superseding the *in silico* prediction.
  - The target substance and the read across analogs are expected to be metabolized similarly as shown by the metabolism simulator.
  - Other structural alerts for toxicological endpoints mentioned above are consistent between the metabolites of the read across analog and the target substance.

Explanation for Cramer Class

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, 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? Yes – Class I Low

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.09.033.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.09.033.

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