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Short review

RIFM fragrance ingredient safety assessment, cyclohexanecarboxylic acid, 1, 4-dimethyl-, methyl ester, *trans*- CAS Registry Number 23250-42-2

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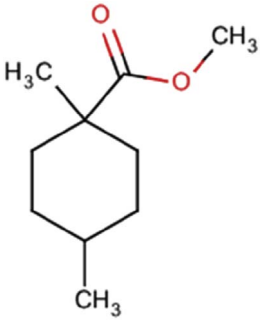
Version: 071317. This version replaces any previous versions.
Name: Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-
CAS Registry Number: 23250-42-2
Additional CAS Numbers*: 23059-38-3 Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *cis*-
*This material is included in this assessment because the materials are a mixture of isomers



Abbreviation 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) 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

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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
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 end-point 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 (cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-) 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 cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- is not genotoxic and provided a MOE > 100 for the repeated dose toxicity endpoint. Data from the read across analog 3-methyl-cyclohexanecarboxylate (CAS # 7605-52-9) show that cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- does not have skin sensitization potential. The developmental and reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The environmental endpoints were evaluated and the material was not found to be PBT as per 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, 1994d; RIFM, 1994e)

Repeated Dose Toxicity: NOAEL = 50 mg/kg/day (RIFM, 1994f)

Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: Not sensitizing (ECHA Dossier; Accessed 1/27/17)

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: 0% (OECD 301D) (RIFM, 1995l)

Bioaccumulation: Screening Level: 96.7 l/kg (US EPA, 2012)

Ecotoxicity: Screening Level: 96 h Algae EC50: 1.760 mg/l (US EPA, 2012)

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 h Algae EC50: 1.760 mg/l (US EPA, 2012)

RIFM PNEC is: 0.1760 μg/L

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: < 1

1. Identification

Chemical Name: Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-	Chemical Name: Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *cis*-
CAS Registry Number: 23250-42-2	**CAS Registry Number:**23059-38-3
Synonyms: Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-; Methyl *trans*-1,4-dimethylcyclohexanecarboxylate; Cyprisate	**Synonyms:** Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *cis*-; Cyprisate
Molecular Formula: $C_{10}H_{18}O_2$	**Molecular Formula:** $C_{10}H_{18}O_2$
Molecular Weight: 170.25	**Molecular Weight:** 170.25
RIFM Number: 6301	**RIFM Number:** 6950

2. Physical data*

1. **Boiling Point:** 206 °C (479 K) [RIFM, 1994e, 203.41 °C [EPI Suite]
2. **Flash Point:** 77 °C [GHS], 77°°C [RIFM, 1993c]

3. **Log K_{OW}**: 3.70 [RIFM, 1993b], 3.51 [EPI Suite]
4. **Melting Point**: < -80 °C (< 193.15 K) [RIFM, 1993a], 1.89 °C [EPI Suite]
5. **Water Solubility:** 61.22 mg/L [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.205 mmHg @ 20 °C [EPI Suite 4.0], 0.304 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

*The physical data for both materials included in this assessment are identical.

3. Exposure***

1. Volume of Use (Worldwide Band): 1–10 metric tons per year	(IFRA, 2011)
2.95th Percentile Concentration in Hydroalcoholics: 0.081%	(RIFM, 2016)
3. Inhalation Exposure*: 0.00042 mg/kg/day or 0.029 mg/day	(RIFM, 2016)
4. Total Systemic Exposure:** 0.0032 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 and Safford et al., 2017).

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

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

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)

CAS # 23250-42-2		
Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I*	I	II
CAS # 23059-38-3		
Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I*	II	II

*See Appendix for explanation.

2. **Analogs Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** 3-Methyl-cyclohexanecarboxylate (CAS# 7605-52-9)
   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)

Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- and Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *cis*-are not reported to occur in food by the VCF*.

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, 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

Neither material is pre-registered as of 7/13/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *cis*- (CAS # 23059-38-3) was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2015). The mutagenic activity of cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- (CAS # 23250-42-2) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 1994d). Under the conditions of the study, cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-was not mutagenic in the Ames test.

The clastogenicity of cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- (CAS # 23250-42-2) was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral

blood lymphocytes were treated with cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-in DMSO at concentrations up to 150 μg/mL in the presence and absence of exogenous metabolic activation. Cells were treated for 3, 19, and 43 h. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, either with or without S9 metabolic activation (RIFM, 1994b). Under the conditions of the study, cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-was considered to be non-clastogenic to human cells.

Based on the data available, cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- (CAS # 23250-42-2) does not present a concern for genotoxic potential.

Additional References: RIFM, 1992b.

Literature Search and Risk Assessment Completed on: 1/14/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-. A 28-day oral gavage study was conducted with test material, cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-. Groups of 5 SD rats/sex/dose were administered test material at dose levels of 0 (corn oil), 15, 150 or 1000 mg/kg/day. Additional satellite groups of 5 rats/sex were administered the vehicle control or test material at 1000 mg/kg/day to investigate the potential effect of cyprisate (trans) to cause α2μ-globulin nephropathy. Salivation was reported among the mid dose group female and high dose group animals. Ocular and/or nasal discharge was more common among high dose group rats as compared to controls. Ataxia, lethargy, tremors, hunched posture and barbering were observed among high dose group animals. Clinical chemistry-related alterations included a statistically significant increase in plasma alanine aminotransferase activity among high dose group males and females and a significant increase in alkaline phosphatase activity among females. A significant decrease in plasma pseudocholinesterase and 5'nucleotidase activities were also seen in high dose group female rats. Plasma triglyceride levels were significantly increased among animals of the high dose group. High dose group animals had an increase in absolute and relative liver weights and males of the mid dose group also had an increase in relative liver weights. Liver weight increases can be considered to be adaptive provided there is lack of histopathological evidence (necrosis, fibrosis, inflammation, and steatotic vacuolar degeneration) showing liver cell damage and clinical chemistry alterations (Hall et al., 2012). Pitting of the liver was reported during necropsy. Hepatocyte hypertrophy was seen among high dose group animals. An increase in hepatocyte cytoplasmic rarefaction was observed in high dose group animals and males of the mid dose group. Absolute and relative kidney weights were increased among high dose group males and relative kidney weights were increased among mid dose group animals. Microscopic alterations, characteristic of α2μ-globulin nephropathy were observed among mid and high dose group males. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990). Thus, the NOAEL was considered to be 150 mg/kg/day, based on alterations in clinical observation parameters, clinical chemistry and alterations in liver weights and histopathology among the high dose group animals (RIFM, 1994a).

A default safety factor of 3 was used when deriving a NOAEL from a 28 day study. The safety factor has been approved by the Expert Panel for Fragrance Safety* (ECHA, *REACH, Technical Guidance on information requirements and chemical safety assessment Chapter R.8: characterization if dose-response for human health (http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf),* the ECETOC *Technical report No. 110 (http://members.ecetoc.org/Documents/Document/20110131112906-ECETOC_Technical_Report_110.pdf) and the* SCCS *notes of guidance for the testing of cosmetic substances and their safety evaluation 9th revision (http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf)*).

Thus, the derived NOAEL for the repeated dose toxicity data is 150/3 or 50 mg/kg/day.

Therefore, the cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- MOE for the repeated dose toxicity endpoint can be calculated by dividing the cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- NOAEL in mg/kg/day by the total systemic exposure to cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-, 50/0.0032 or 15625.

In addition, the total systemic exposure to cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- (3.2 μg/kg/day) is below the TTC (30 μg/kg/day) for the repeated dose toxicity endpoint of a Cramer Class I material 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: 01/17/2017.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- or any read across materials. The total systemic exposure to cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- or any read across materials that can be used to support the developmental and reproductive toxicity endpoints. The total systemic exposure to cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- (3.2 μg/kg/day) is below the TTC (30 μg/kg/day) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/17/2017.

10.1.4. Skin sensitization

Based on the existing data for cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- and read across to 3-methyl-cyclohexanecarboxylate (CAS# 7605-52-9), cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data for cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- and read across to 3-methyl-cyclohexanecarboxylate (CAS# 7605-52-9; see section V), cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-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 (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig maximization test an 80/20 mixture of cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester and methyl 1,3-dimethyl cyclohexane carboxylate (cyprisate) was found to be negative (RIFM, 1992c; RIFM, 1992a). In a murine local lymph node assay (LLNA), read across 3-methyl-cyclohexanecarboxylate was found to be non-sensitizing up to 50% (12500 μg/cm^2) (ECHA REACH Dossier; Accessed 1/27/17). Based on weight of evidence from structural analysis, animal data and read across, cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, trans -does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/27/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV absorption spectra, cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-in experimental models. UV absorption spectra indicate no significant absorption between 290 and 500 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009). Based on lack of absorbance, cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on:12/02/15.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-, 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 cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-. Based on the Creme RIFM model, the inhalation exposure is 0.028 mg/day. This exposure is 50.0 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: None.

Literature Search and Risk Assessment Completed on: 12/14/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-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) 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. 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). Following the RIFM Environmental Framework, cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-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 ver 4.1 did not identify cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-as either being possibly persistent nor 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 ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

10.2.2. Risk assessment

Based on current Volume of Use (2011), cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. **RIFM, 1995**: A biodegradation study was conducted according to the OECD 301D method. After 28 days no biodegradation was observed.

10.2.2.2. Ecotoxicity. **RIFM, 1994c**: An algae growth inhibition test was conducted according to the OECD 201 method. The 72 h EC50 was reported to be 32 mg/l and 45 mg/l for growth inhibition and growth rate, respectively.

RIFM, 2003: An algae growth inhibition test was conducted according to the OECD 201 method. The 72 h EC50 was reported to be 18 mg/l and 24 mg/l for growth inhibition and growth rate, respectively.

RIFM, 1994f: A *Daphnia magna* immobilization study was conducted according to the EEC Directive 92/69 Part C method under semi-static conditions. The 48 h EC50 was reported to be 33 mg/l.

RIFM, 1994g: A 96-h acute toxicity semi-static study was conducted with carp (*Cyprinus carpio*) according to the EEC Directive 96/69 Part C method. The LC50 was reported to be 24 mg/l.

10.2.2.3. Other available data. No additional data available.

11. Risk assessment refinement

Since cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	7.620 mg/l			1,000,000	0.00762 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.973 mg/l	5.255 mg/l	1.760 mg/l	10,000	0.176 µg/l	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	6.112 mg/l	3.991 mg/l	5.298 mg/l			Neutral Organic SAR (Baseline toxicity)

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.7	3.7
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 further assessment is necessary.

The RIFM PNEC is 0.1760 µg/L. The revised PEC/PNECs for EU and NA are < 1 and, therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on:12/2/2015.

12. 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.2017.11.017.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.11.017.

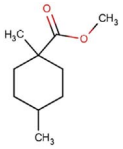
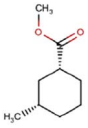
Appendix

Read across justification

Methods

The read across analog was 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, the appropriate read across analog 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 analog were calculated using EPI Suite™ v4.11 developed by US EPA (US EPA, 2012).
- 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 analog were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target material	Read across material
Principal Name	Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*-	Cyclohexanecarboxylic acid, 3-methyl, methyl ester, (1R,3S)-rel-
CAS No.	23250-42-2	7605-52-9
Structure		
Similarity (Tanimoto score)		0.67
Read across endpoint		• Skin sensitization
Molecular Formula	$C_{10}H_{18}O_2$	$C_9H_{16}O_2$
Molecular Weight	170.25	156.23
Melting Point (°C, EPISUITE)	1.89	−18.45
Boiling Point (°C, EPISUITE)	203.41	193.97
Vapor Pressure (Pa @ 25°C, EPISUITE)	40.6	64.9
Log Kow (KOWWIN v1.68 in EPISUITE)	3.7[1]	3.06
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	61.22	173.4
J_{max} (mg/cm^2/h, SAM)	118.966	14.051
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	5.62E-004	4.23E-004
Skin Sensitization		
Protein binding by OASIS v1.4	• Acylation	• No alert found
Protein binding by OECD	• Acylation	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.4	• Acylation	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (moderate reliability)	• Sensitizer (moderate reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

[1]RIFM, 1993b.

Summary

There are insufficient toxicity data on cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- (CAS # 23250-42-2). Hence, *in silico* evaluation was conducted to determine a read across analog for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, cyclohexanecarboxylic acid, 3-methyl, methyl ester, (1R, 3S)-rel- (CAS # 7605-52-9) was identified as a read across material with data for its respective toxicoloigcal endpoints.

Conclusion/Rationale

- Cyclohexanecarboxylic acid, 3-methyl, methyl ester, (1R, 3S)-rel- (CAS # 7605-52-9) could be used as a structurally similar read across analog for the target material cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, *trans*- (CAS # 23250-42-2) for the skin sensitization endpoint.
  - o The target substance and the read across analog are structurally similar and belong to the structural class of esters.
  - o The target substance and the read across analog are both alkyl substituted cyclohexane carboxylic acid methyl esters.
  - o The key difference between the target substance and the read across analog is the methyl substitution on cyclohexane ring. The differences in structure between the target substance and the read across analog do not raise additional structural alerts, so the structural differences are not

relevant from a toxicological perspective.

- o Similarity between the target substance and the read across analog is indicated by the Tanimoto score presented in the above table. The Tanimoto score is mainly driven by the saturated esters fragment. The differences in the structure which are responsible for a Tanimoto score < 1 are not relevant from a toxicological perspective.
- o The target substance and the read across analog have similar physical chemical properties. The J_{max} value of the target and the read across analog appear to be different, but with the calculated J_{max}, the read across analog substance and the target are predicted to have skin absorption up to 80%.
- o Any other differences in some of the physical chemical properties of the target substance and the read across analog are toxicologically insignificant for the skin sensitization endpoint.
- o Structural alerts for the skin sensitization toxicity endpoint are consistent between the target substance and the read across analog as seen in the table above. According to the CAESAR model, both the target substance and the read across analog are predicted to be sensitizers with moderate reliability. This prediction is superseded by the negative sensitization data for the read across analog.
- o The target substance and the read across analog are expected to be metabolized similarly as shown by the metabolism simulator.
- o The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read across analog and the target substance.

Explanation of Cramer classification

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

Q1 Normal constituent of the body? No
Q2 Contains functional groups associated with enhanced toxicity? No
Q3 Contains elements other than C, H, O, N, and divalent S? No;
Q4 Elements not listed in Q3 occur only as a Na, K, Ca, Mg, N salt, sulfamate, sulfonate, sulfate, hydrochloride? No
Q6 Benzene derivative with certain substituents? No
Q7 Heterocyclic? No;
Q16 Common terpene? (see Cramer et al., 1976 for detailed explanation)? No
Q17 Readily hydrolyzed to a common terpene? No
Q19 Open chain? No;
Q23 Aromatic? No
Q24 Monocarbocyclic with simple substituents? No
Q18 One of the list? (see Cramer et al., 1976 for detailed explanation on list of categories) No
Class Low (Class I).

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