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Short review

RIFM fragrance ingredient safety assessment, 1-cyclohexylethyl butyrate, CAS Registry Number 63449-88-7

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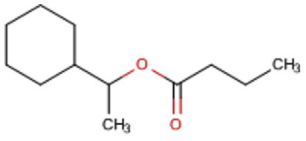

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(*continued*)

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
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
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

RIFM's Expert Panel* 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).

*RIFM's Expert Panel 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.

This material 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 this material is not genotoxic. Data from the suitable read across analogue *d*-cyclocitronellene acetate (CAS # 25225-10-9) show that this material does not have skin sensitization potential. The repeated dose, reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03, 0.03 mg/kg/day and 1.4 mg/day, respectively). The developmental toxicity endpoint was completed using data from the target material which provided a MOE >100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 1978b; RIFM, 2015a)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: Developmental NOAEL = 1000 mg/kg/day. No NOAEL available for reproductive toxicity, the exposure is below the TTC. (RIFM, 1978c)
Skin Sensitization: Not sensitizing (RIFM, 1976; RIFM, 1977c; RIFM, 1977d; RIFM, 1977e; RIFM, 1977b)
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: Screening Level: 2.9 (Biowin 3) (EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 455 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: 96 h Algae EC50: 0.397 mg/L (EpiSuite ver 4.1)
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: 0.397 mg/L (EpiSuite ver 4.1)
RIFM PNEC is: 0.0397 μg/L
- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe <1

1. Identification

1. **Chemical Name:** 1-Cyclohexylethyl butyrate
2. **CAS Registry Number:** 63449-88-7
3. **Synonyms:** Butanoic acid, 1-cyclohexylethyl ester; 1-Cyclohexylethyl butyrate; ｱﾙｷﾙ(C = 1 ~ 4)ｶﾙﾎﾞﾝ酸ｼｸﾛﾍｷｼﾙｴﾁﾙ
4. **Molecular Formula:** $C_{12}H_{22}O_2$
5. **Molecular Weight:** 198.06
6. **RIFM Number:** 5789

2. Physical data

1. **Boiling Point:** 244.94 °C [EPI Suite]
2. **Flash Point:** 95 °C [GHS]
3. **Log K_{OW}:** 4.53 [EPI Suite]
4. **Melting Point:** 7.96 °C [EPI Suite]
5. **Water Solubility:** 5.997 mg/L [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0277 mmHg @ 20 °C [EPI Suite 4.0], 0.0356 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra**: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A colorless to pale yellow clear liquid ** http://www.thegoodscentscompany.com/data/rw1469991.html#toorgano, retrieved 01/13/2017

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.40% (RIFM, 2015b)
3. **Inhalation Exposure*:** 0.0011 mg/kg/day or 0.079 mg/day (RIFM, 2015b)
4. **Total Systemic Exposure**:** 0.0120 mg/kg/day (RIFM, 2015b)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; and Safford et al., 2015; Safford 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; and Safford et al., 2015; Safford 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. **Analogues Selected:**
   a. **Genotoxicity:** *d*-Cyclocitronellene acetate (CAS # 25225-10-9)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** *d*-Cyclocitronellene acetate (CAS # 25225-10-9)
   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)

1-Cyclohexylethyl butyrate is 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

Pre-registered for 2010; No dossier available as of 01/13/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 1-cyclohexylethyl butyrate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 1-Cyclohexylethyl butyrate was assessed in the Bluescreen assay and found negative for genotoxicity with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013). The mutagenic activity of 1-cyclohexylethyl butyrate was assessed in an Ames assay conducted equivalent to OECD 471 TG. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were treated with 1-

cyclohexylethyl butyrate in acetone at 0.001, 0.01, 0.1, 1.0, 5.0 and 10 μl/plate with and without metabolic activation. No significant increase in the number of revertant colonies was observed (RIFM, 1978a,b,c). Under the conditions of the study, 1-cyclohexylethyl butyrate was considered not mutagenic in bacteria. As a weight of evidence approach, read across material *d*-cyclocitronellene acetate (CAS # 25225-10-9) was assessed for mutagenic activity in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia Coli* strain WP2 uvrA were evaluated at concentrations up to 313 μl/plate of *d*-cyclocitronellene acetate in DMSO (dimethyl sulfoxide) in the presence and absence of metabolic activation. No increase in the frequency of revertant colonies was observed in the any of the strains at the concentrations tested (RIFM, 2008). Under the conditions of the study, *d*-cyclocitronellene acetate is not mutagenic in bacteria and this can be extended to 1-cyclohexylethyl butyrate.

The clastogenicity of 1-cyclohexylethyl butyrate was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral lymphocytes were treated with 1-cyclohexylethyl butyrate in DMSO at concentrations up to 300 μg/ml in the presence and absence of metabolic activation (S-9). No statistically significant increases in the frequency of cells with micronuclei were observed (RIFM, 2015a). Under the conditions of the study, 1-cyclohexylethyl butyrate was considered not clastogenic.

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

Additional References: None.

Literature Search and Risk Assessment Completed on: 12/20/15.

10.1.2. Repeated dose toxicity

There is insufficient repeated dose toxicity data on 1-cyclohexylethyl butyrate or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC) at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 1-cyclohexylethyl butyrate or any of the read across materials that can be used to support the repeated dose toxicity endpoint. A gavage range finding study was conducted on 1-cyclohexylethyl butyrate for a period of 4 weeks at doses of 0, 100, 300, 1000 and 3000 mg/kg/day. There was no adverse toxicity reported up to the highest dose tested. However, in the absence of histopathological and blood chemistry data no conclusion can be derived regarding the NOAEL for 1-cyclohexylethyl butyrate (RIFM, 1978a). The total systemic exposure to 1-cyclohexylethyl butyrate (12 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/22/2015.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 1-cyclohexylethyl butyrate is adequate for the developmental toxicity endpoint at the current level of use.

There is insufficient reproductive toxicity data on 1-cyclohexylethyl butyrate or any of the read across materials. The exposure is below the Threshold of Toxicological Concern (TTC) at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental toxicity data on 1-cyclohexylethyl butyrate. A gavage developmental toxicity study was conducted on pregnant female Charles River CD rats at 0, 100, 300, 1000 and 3000 mg/kg/day from gestational days 6–15. The NOAEL for developmental toxicity was determined to be 1000 mg/kg/day based on decreased fetal body weights (RIFM, 1978c). There were no teratogenic effects observed even at dosages that caused maternal toxicity. **Therefore, the 1-cyclohexylethyl butyrate MOE for the developmental toxicity endpoint can be calculated by dividing the 1-cyclohexylethyl butyrate NOAEL in mg/kg/day by the total systemic exposure to 1-cyclohexylethyl butyrate, 1000/0.012 or 83333.**

In addition, the total systemic exposure to 1-cyclohexylethyl butyrate (12 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the developmental toxicity endpoint at the current level of use.

There are no reproductive toxicity data on 1-cyclohexylethyl butyrate or any of the read across materials that can be used to support the reproductive toxicity endpoint. **The total systemic exposure to 1-cyclohexylethyl butyrate (12 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the reproductive toxicity endpoint at the current level of use.**

Additional References: None.

Literature Search and Risk Assessment Completed on: 05/31/2016.

10.1.4. Skin sensitization

Based on the existing limited data and read across *d*-cyclocitronellene acetate (CAS # 25225-10-9), 1-cyclohexylethyl butyrate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data and read across to *d*-cyclocitronellene acetate (CAS # 25225-10-9; See Section 5), 1-cyclohexylethyl butyrate does not present a concern for skin sensitization. The chemical structures of 1-cyclohexylethyl butyrate and *d*-cyclocitronellene acetate indicate that they would not be expected to be reactive to skin proteins directly (Roberts et al., 2007; Toxtree 2.6.6; OECD Toolbox v3.3). No predictive animal tests exist for 1-cyclohexylethyl butyrate. However, in a guinea pig maximization test read across material *d*-cyclocitronellene acetate was found to be non-sensitizing (RIFM, 1981). A human repeated insult patch test with neat 1-cyclohexylethyl butyrate did not exhibit reactions indicative of sensitization (RIFM, 1976). Moreover, no results indicative of a sensitization potential were reported with read across material *d*-cyclocitronellene acetate (RIFM, 1976; RIFM, 1982; RIFM, 1977c; RIFM, 1977d; RIFM, 1977e; RIFM, 1977b). Based on weight of evidence from available human data and read across material, 1-cyclohexylethyl butyrate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/31/15.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 1-cyclohexylethyl butyrate 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 1-cyclohexylethyl butyrate in experimental models. 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 $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). Based on lack of absorbance, 1-cyclohexylethyl butyrate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 5/26/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 1-cyclohexylethyl butyrate, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are limited inhalation data available on 1-cyclohexylethyl butyrate. Based on the Creme RIFM model, the inhalation exposure is 0.079 mg/day. This exposure is 17.7 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, 1977a.

Literature Search and Risk Assessment Completed on: 05/31/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 1-cyclohexylethyl butyrate 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 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, 1-cyclohexylethyl butyrate 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 1-cyclohexylethyl butyrate 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).

10.2.2. Risk assessment

Based on current Volume of Use (2011), 1-cyclohexylethyl butyrate presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. None.

10.2.2.2. Ecotoxicity. None

10.2.2.3. Other available data

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

10.2.3. 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)**	1.682 mg/L			1,000,000	0.001682 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.879 mg/L	1.393 mg/L	0.397 mg/L	10,000	0.0397 μg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.864 mg/L	0.620 mg/L	1.215 mg/L			Neutral Organic SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.53	4.53
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.0397 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: 9/16/15

11. Literature Search*

- RIFM database: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHAhttp://echa.europa.eu/
- NTPhttp://tools.niehs.nih.gov/ntp_tox/index.cfm
- OECD Toolbox
- SciFinderhttps://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- PUBMEDhttp://www.ncbi.nlm.nih.gov/pubmed
- TOXNEThttp://toxnet.nlm.nih.gov/
- IARC(http://monographs.iarc.fr)
- OECD SIDShttp://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- EPA Actorhttp://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- US EPA HPVIShttp://www.epa.gov/hpv/hpvis/index.html
- US EPA Robust Summaryhttp://cfpub.epa.gov/hpv-s/
- Japanese NITEhttp://www.safe.nite.go.jp/english/db.html
- Japan Existing Chemical Data Basehttp://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- Googlehttps://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.2017.04.031.

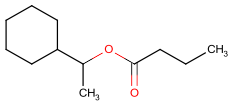
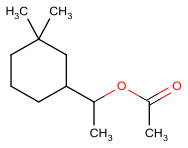
Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.04.031.

Appendix

Methods

- The identified read across analogue were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints. (Rogers and Hahn, 2010).
- The physicochemical properties of the target substance and the read across analogue were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- J_{max} were calculated using RIFM skin absorption model (SAM), 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 analogues were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Strategies on finding and using read across are outlined in Schultz et al. (2015).

	Target material	Read across material
Principal Name	1-Cyclohexylethyl butyrate	d-Cyclocitronellene acetate
CAS No.	63449-88-7	25225-10-9
Structure		
Similarity (Tanimoto score)	1	0.42991
Read across endpoint		• Genotoxicity (as weight of evidence) • Skin sensitization
Molecular Formula	$C_{12}H_{22}O_2$	$C_{12}H_{22}O_2$
Molecular Weight	198.31	198.31
Melting Point (°C, EPISUITE)	7.96	13.46

Boiling Point (°C, EPISUITE)	244.94	230.13
Vapor Pressure	4.75	10.4
(Pa @ 25°C, EPISUITE)		
Log Kow **(KOWWIN v1.68 in EPISUITE)**	4.53	4.42
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	5.997	7.462
J_{max} (mg/cm^2/h, SAM)	0.829838	0.980492
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.00E+002	1.00E+002
Genotoxicity		
DNA binding (OASIS v 1.1 QSAR Toolbox 3.4)	• No alert found	• AN2, SN1, SN2
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Carcinogenicity (Genotox and non-Genotox) alerts (ISS)	• No alert found	• No alert found
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**	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor
Oncologic Classification	• Not classified	• Not classified
Sensitization		
Protein binding by OASIS v1.1	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found
Protein binding potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
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 (good reliability)	• Sensitizer (good reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1 • 12 metabolites from Rat S9 simulator. • Aldehydes, anionic surfactants, esters, Schiff base formation, SN2.	See Supplemental Data 2 • 10 metabolites from Rat S9 simulator. • Aldehydes, esters, Schiff base formation, SN2.

Summary

There are insufficient toxicity data on 1-cyclohexylethyl butyrate (CAS # 63449-88-7). Hence *in-silico* evaluation was conducted by determining suitable read across analogues for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogue *d*-cyclocitronellene acetate (CAS # 25225-10) was identified as proper read across materials with data for their respective toxicity end points.

Conclusion/Rationale

- *d*-Cyclocitronellene acetate (CAS # 25225-10) can be used as a structurally similar read across analogue for the target material 1-cyclohexylethyl butyrate (CAS # 63449-88-7) for the genotoxicity and skin sensitization endpoints.
  - o The target substance and the read across analogue are structurally similar and belong to the structural class of esters.
  - o The key difference between the target substance and the read across analogue is that the target has 3 degrees of unsaturation while read across has 2.5 degrees of unsaturation. The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.
  - o The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the cyclohexyl ethyl fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevent from a toxicological endpoint perspective.
  - o The target substance and the read across analogue have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for the skin sensitization toxicological endpoint.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for the genotoxicity and skin sensitization endpoints are consistent between the target substance and the read across analogue as seen in the table above.
  - o The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for the skin sensitization toxicological endpoint are consistent between the metabolites of the read across analogue and the target substance.
  - o The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

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