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Short Review

RIFM fragrance ingredient safety assessment, hexyl 2-hydroxypropionate, CAS Registry Number 20279-51-0

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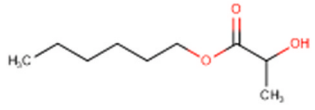

Name: Hexyl 2-hydroxypropionate
CAS Registry Number: 20279-51-0

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
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

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NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use, but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

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

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

Summary: The existing information supports the use of this material as described in this safety assessment.

Hexyl 2-hydroxypropionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl lactate (CAS # 97-64-3) show that hexyl 2-hydroxypropionate is not expected to be genotoxic, provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints, and show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; hexyl 2-hydroxypropionate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; the exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated. For the hazard assessment based on the screening data, hexyl 2-hydroxypropionate is not persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, hexyl 2-hydroxypropionate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: Ethyl lactate; ECHA, 2019)
Repeated Dose Toxicity: NOAEL = 51.9 mg/kg/day.	(Clary et al., 1998)
Reproductive Toxicity: Developmental toxicity: 75 mg/kg/day Fertility: 600 mg/kg/day.	(ECHA REACH Dossier: Ethyl Lactate; ECHA, 2019)

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Skin Sensitization: Not a concern for skin sensitization at the current, declared use levels.	(ECHA REACH Dossier: Ethyl (S)-2-hydroxypropionate; ECHA, 2011)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.4 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 6.956 L/kg	(EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Not applicable

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; no Volume of Use in 2015 reported for Europe and North America

1. Identification

1. **Chemical Name:** Hexyl 2-hydroxypropionate
2. **CAS Registry Number:** 20279-51-0
3. **Synonyms:** Hexyl lactate; Propanoic acid, 2-hydroxy-, hexyl ester; Hexyl 2-hydroxypropanoate; Hexyl 2-hydroxypropionate
4. **Molecular Formula:** $C_9H_{18}O_3$
5. **Molecular Weight:** 174.24
6. **RIFM Number:** 1371

2. Physical data

1. **Boiling Point:** 244.52 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 1.78 (EPI Suite)
4. **Melting Point**: 17.65 °C (EPI Suite)
5. **Water Solubility:** 5719 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00463 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Toothpaste:** 0.015% (RIFM, 2017)

   No reported use in hydroalcoholics

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.00056 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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; Safford et al., 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
I	I	I

2. **Analogs** Selected:
   a. **Genotoxicity:** Ethyl lactate (CAS # 97-64-3)
   b. **Repeated Dose Toxicity:** Ethyl lactate (CAS # 97-64-3)
   c. **Reproductive Toxicity:** Ethyl lactate (CAS # 97-64-3)
   d. **Skin Sensitization:** Ethyl lactate (CAS # 97-64-3)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

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

Hexyl 2-hydroxypropionate is reported to occur in the following foods by the VCF*:

Bilberry wine.
Cider (apple wine).
Grape brandy.
Sherry.
Wine.

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

9. REACH dossier

Pre-registered for 2010; no dossier available as of 11/14/19.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, hexyl 2-hydroxypropionate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Hexyl 2-hydroxypropionate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2014). There are no studies assessing the mutagenic activity of hexyl 2-hydroxypropionate; however, read-across can be made to ethyl lactate (CAS # 97-64-3; see Section VI). The mutagenic activity of ethyl lactate 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 TA97a, TA98, TA100, TA1535, and TA102 were treated with ethyl lactate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2019). Under the conditions of the study, ethyl lactate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of hexyl 2-hydroxypropionate. However, read-across can be made to ethyl lactate (CAS # 97-64-3; see Section VI).

The clastogenic activity of ethyl lactate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with ethyl lactate at concentrations up to 10 mM in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 10 mM in the presence and absence of metabolic activation. Ethyl lactate did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (ECHA, 2019). Under the conditions of the study, ethyl lactate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, ethyl lactate does not present a concern for genotoxic potential, and this can be extended to hexyl 2-hydroxypropionate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/23/19.

11.1.2. Repeated dose toxicity

The MOE for hexyl 2-hydroxypropionate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on hexyl 2-hydroxypropionate. Read-across material ethyl lactate (CAS # 97-64-3; see Section VI) has sufficient repeated dose toxicity data.

In an OECD TG 412 and GLP-compliant repeated dose toxicity study, 5 rats/sex/dose (strain not reported) were exposed to ethyl lactate via inhalation at concentrations of 0, 150, 600, and 2500 mg/m^3 (converted using the standard minute volume [MV] and body weights for Sprague Dawley rats; equivalent to 38.9, 155.6, and 648.3 mg/kg/day, respectively) for 28 days (6 h/day, 5 days/week). No treatment-related clinical signs or effects on hematological parameters were reported at any dose level. At the high dose (648.3 mg/kg/day), significantly decreased bodyweight gain and food consumption (sex not specified) were reported. Based on decreased bodyweight gain and food consumption at the highest dose, the NOAEL for this study was considered to be 155.6 mg/kg/day (Clary et al., 1998).

In an OECD TG 412 and GLP-compliant repeated dose toxicity study, 5 rats/sex/dose (strain not reported) were exposed to ethyl lactate via

inhalation at concentrations of 0, 25, 75, and 200 mg/m^3 (converted using the standard MV and body weights for Sprague Dawley rats; equivalent to 6.48, 19.5, and 51.9 mg/kg/day, respectively) for 28 days (6 h/day, 5 days/week). No treatment-related adverse effects were reported for any of the parameters evaluated up to the highest tested dose of 51 mg/kg/day. Therefore, the NOAEL for this study was considered to be 51.9 mg/kg/day (Clary et al., 1998).

In an OECD TG 422 and GLP-compliant study, 10 male Wistar rats/dose and 13 female Wistar rats/dose were administered ethyl lactate via gavage at doses of 0 (vehicle control: olive oil), 100, 500, and 800 mg/kg/day for 28 days (males) or 63 days (females). Additionally, recovery groups of 5 rats/sex/dose were maintained for an additional 2 weeks at 0 and 800 mg/kg/day; however, little information was available about the recovery group, other than the functional battery observation tests, which revealed no treatment-related abnormalities at the end of the recovery period. After 10 days of treatment, doses were reduced to 75, 300, and 600 mg/kg/day due to increased mortality in high-dose females (exceeding 10%). Mortality was reported in 2 males and 1 female (dose groups not specified) in the first 2 weeks of dosing, but these deaths were not considered to be treatment-related. There were no treatment-related adverse effects reported for clinical findings, functional observational battery, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights, necropsy, or histopathology at any of the doses. Based on no adverse effects seen up to the highest dose, the NOAEL for this study was reported to be 600 mg/kg/day (ECHA, 2019).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. Thus, the derived NOAEL for the repeated dose toxicity data is 155.6/3 or 51.9 mg/kg/day.

Therefore, the MOE can be calculated by dividing the NOAEL (in mg/kg/day) for ethyl lactate by the total systemic exposure (in mg/kg/day) of hexyl 2-hydroxypropionate, 51.9/0.00056 or 92679.

In addition, the total systemic exposure to hexyl 2-hydroxypropionate (0.56 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose 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: NIH, 2005.

Literature Search and Risk Assessment Completed On: 12/05/19.

11.1.3. Reproductive toxicity

The MOE for hexyl 2-hydroxypropionate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on hexyl 2-hydroxypropionate. Read-across material ethyl lactate (CAS # 97-64-3; see Section VI) has sufficient repeated dose toxicity data.

In an OECD 422/GLP study groups of 10 males and 13 female Wistar rats/sex/dose were administered the test material at doses of 0 (olive oil), 75, 300, or 600 mg/kg/day. The males were treated for 14 days pre-mating and 14 days during mating. The females were treated for 14 days during pre-mating, 14 days during mating, 22 days during gestation, and 13 days during lactation. An additional satellite group of 5 rats/sex were treated with either the vehicle or the high dose and remained untreated for 14 days after the end of treatment duration. Mortality was reported among females (at 800 mg/kg/day for 2 females during the first week and 1 female during the second week of treatment), due to which the dose was reduced for the remainder of the treatment duration. Following dose reduction, there were no clinical signs or mortality reported among treated animals. There were no treatment-related effects on parental reproductive performance, gestation length, parturition, or reproductive organs among treated animals. Based on this, the NOAEL for parental fertility toxicity was considered to be 600 mg/kg/day (ECHA, 2019).

Therefore, the MOE for the fertility toxicity endpoint is equal to the ethyl lactate NOAEL in mg/kg/day divided by the total systemic exposure to hexyl 2-hydroxypropionate, 600/0.00056 or 1071429.

In the same OECD 422 study described above, a dose-dependent, statistically significant decrease in the anogenital index (AGI; anogenital distance/body weights) was reported among male pups (considered to be feminization in the low- and mid-dose male pups). This alteration in AGI was considered to be a specific developmental effect of prenatal exposure to the test material. Records of pre-implantation and early post-implantation loss (4 non-pregnant females and 2 pregnant females that failed to deliver at the low dose along with 2 non-pregnant and 2 pregnant females that failed to deliver at mid dose) among the mid- and low-dose groups were considered to be treatment-related. An alteration in the number of live pups per dam on postnatal days 0 and 4 along with changes in litter weight at birth among mid-dose offspring were also considered to be treatment-related effects. Further, high-dose male pups were reported to have a statistically significant increase in body weights on day 13 postpartum. In addition, there was a statistically significant reduction in T4 levels among male and female offspring that was not accompanied by an alteration in mean relative thyroid weights or histopathology. Hence, this was not considered to be biologically significant. Thus, considering all the data, the LOAEL for developmental toxicity was considered to be 75 mg/kg/day (ECHA, 2019). A NOAEL of 7.5 mg/kg/day was considered for developmental toxicity by dividing the LOAEL of 75 mg/kg/day by a safety factor of 10 (ECHA, 2019).

Therefore, the MOE for the developmental toxicity endpoint is equal to the ethyl lactate NOAEL in mg/kg/day divided by the total systemic exposure to hexyl 2-hydroxypropionate, 7.5/0.00056 or 13393.

In addition, the total systemic exposure to hexyl 2-hydroxypropionate (0.56 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/19/19.

11.1.4. Skin sensitization

Based on read-across material ethyl lactate (CAS # 97-64-3), hexyl 2-hydroxypropionate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. No data skin sensitization studies are available for hexyl 2-hydroxypropionate. Based on the existing data and read-across material ethyl lactate (CAS # 97-64-3; see Section VI), hexyl 2-hydroxypropionate is not considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material ethyl lactate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and LuSens (ECHA, 2019). In a murine local lymph node assay (LLNA), additional read-across material (isomer) ethyl (L)-lactate was found to be negative up to 100% (ECHA, 2011). In a human maximization test, no skin sensitization reactions were observed with read-across material ethyl lactate (RIFM, 1976).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material ethyl lactate, hexyl 2-hydroxypropionate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: Jordan and Dahl, 1971; Marot and Grosshans, 1987

Literature Search and Risk Assessment Completed On: 12/18/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, hexyl 2-hydroxypropionate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for hexyl 2-hydroxypropionate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, hexyl 2-hydroxypropionate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/22/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for hexyl 2-hydroxypropionate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on hexyl 2-hydroxypropionate. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 14000 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: 12/19/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of hexyl 2-hydroxypropionate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, hexyl 2-hydroxypropionate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify hexyl 2-hydroxypropionate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

Risk Assessment: Not applicable.

11.2.1.1. Key studies

11.2.1.1.1. Biodegradation. No data available.

11.2.1.1.2. Ecotoxicity. No data available.

11.2.1.2. Other available data. Hexyl 2-hydroxypropionate has been pre-registered for REACH with no additional data available at this time.

Risk Assessment Refinement: Not applicable.

Literature Search and Risk Assessment Completed On: 12/09/19.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/20.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no

known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111851.

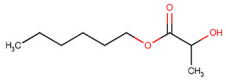
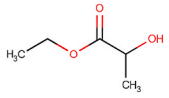
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Hexyl 2-hydroxypropionate	Ethyl lactate
CAS No.	20279-51-0	97-64-3
Structure		
Similarity (Tanimoto Score)		0.62
Read-across Endpoint		• Genotoxicity • Repeated dose toxicity • Reproductive toxicity • Skin sensitization
Molecular Formula	$C_9H_{18}O_3$	$C_5H_{10}O_3$
Molecular Weight	174.24	118.13
Melting Point (°C, EPI Suite)	17.65	−27.76
Boiling Point (°C, EPI Suite)	244.52	154.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	6.17E-001	5.00E+002
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	1.78	−0.18
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.27E+004	1.00E+006
J_{max} (μg/cm^2/h, SAM)	105.692	2193.282
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.52E+001	5.91E-002
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Carcinogenicity (ISS)	• No alert found	• No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor
Oncologic Classification	• Not classified	• Not classified
Repeated Dose Toxicity		
Repeated dose (HESS)	• Not categorized	• Not categorized
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Toxicant (good reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (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 (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on hexyl 2-hydroxypropionate (CAS # 20279-51-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, ethyl lactate (CAS # 97-64-3) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Ethyl lactate (CAS # 97-64-3) was used as a read-across analog for the target material hexyl 2-hydroxypropionate (CAS # 20279-51-0) for the genotoxicity, repeated dose toxicity, reproductive toxicity, and skin sensitization endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of saturated esters.
  - The target material and the read-across analog share a lactic acid moiety.
  - The key difference between the target material and the read-across analog is that the target material has a hexanol alcohol moiety whereas the read-across analog has an ethanol alcohol moiety. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and the read-across analog have an H-acceptor-path3-H-acceptor alert within *In Vivo* mutagenicity (Micronucleus, ISS), which is due to the O–C–CH–OH molecular framework. This alert explores the possibility that a chemical interacts with DNA and/or proteins via non-covalent binding, such as DNA intercalation or groove-binding. Among the descriptors potentially accounting for non-covalent interactions, the present molecular framework representing 2 bonded atoms connecting 2 H bond acceptors resulted in an increased sensitivity/specificity for what concerns the micronucleus training set. The data described in the genotoxicity section show that there are no concerns for genotoxicity. Therefore, the predictions are superseded by the data.
  - The read-across is classified as a toxicant for developmental toxicity (CAESAR). The data described in the reproductive toxicity section show that the MOE is adequate at the current level of use. Therefore, the predictions are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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