



Short Review

RIFM fragrance ingredient safety assessment, ethyl pyruvate, CAS Registry Number 617-35-6

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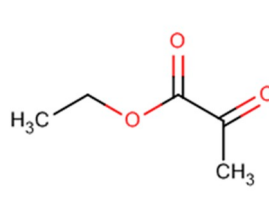
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Version: 111518. This version replaces any previous versions.

Name: Ethyl pyruvate CAS Registry Number: 617-35-6



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., 2015a, 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

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IFRA - The International Fragrance Association
 LOEL - Lowest Observable Effect Level
 MOE - Margin of Exposure
 MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
 NA - North America
 NESIL - No Expected Sensitization Induction Level
 NOAEC - No Observed Adverse Effect Concentration
 NOAEL - No Observed Adverse Effect Level
 NOEC - No Observed Effect Concentration
 NOEL - No Observed Effect Level
 OECD - Organisation for Economic Co-operation and Development
 OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
 PBT - Persistent, Bioaccumulative, and Toxic
 PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
 QRA - Quantitative Risk Assessment
 REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
 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.

Ethyl pyruvate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on the target material and from read-across materials ethyl alcohol (CAS # 64-17-5) and pyruvic acid (CAS # 127-11-3) show that ethyl pyruvate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to ethyl pyruvate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the DST for non-reactive materials (900 µg/cm²); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; ethyl pyruvate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; ethyl pyruvate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (Andersen and Jensen, 1984; OECD SIDS: Ethanol; OECD, 2004)

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.

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

Skin Sensitization: Not a sensitization concern. Exposure is below DST.

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:

Critical Measured Value: 97% (OECD 301F) (ECHA REACH Dossier: Ethyl pyruvate; ECHA, 2018)

Bioaccumulation:

Screening-level: 3.162 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 8599 mg/L (RIFM Framework; Salvito et al., 2002)

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: Fish LC50: 8599 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 8.599 µg/L

•Revised PEC/PNECs (2015 IFRA VoU): North America and Europe (not reported): not applicable; cleared at screening-level

1. Identification

- 1. Chemical Name:** Ethyl pyruvate
- 2. CAS Registry Number:** 617-35-6
- 3. Synonyms:** Ethyl acetylformate; Ethyl α-ketopropionate; Ethyl 2-oxopropanoate; Ethyl pyrroacemate; Propanoic acid, 2-oxo-, ethyl ester; Ethyl pyruvate
- 4. Molecular Formula:** C₅H₈O₃
- 5. Molecular Weight:** 116.12

6. RIFM Number: 6805

7. Stereochemistry: Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. Boiling Point: 144 °C (FMA Database), 147.34 °C (EPI Suite)

2. Flash Point: 115 °F; CC (FMA Database)

3. Log K_{ow}: -0.47 (EPI Suite)

4. **Melting Point:** -31.21 °C (EPI Suite)
5. **Water Solubility:** 259000 mg/L (EPI Suite)
6. **Specific Gravity:** 1.060 (FMA Database)
7. **Vapor Pressure:** 2.28 mm Hg @ 20 °C (EPI Suite v4.0), 3.18 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:** Arctander, Volume I, 1969: Colorless liquid. Sweet, floral-fruity, warm odor of poor tenacity. Sweet, warm, and slightly spicy-caramellic taste with a trace of a fruity note.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Shampoo products:** 0.0082% (RIFM, 2016)

(No reported use in Hydroalcoholics).

3. **Inhalation Exposure*:** 0.0000001 mg/kg/day or 0.0000064 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00012 mg/kg/day (RIFM, 2016)

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. **Analogs Selected:**
 - a. **Genotoxicity:** Ethyl alcohol (CAS # 64-17-5) and Pyruvic acid (CAS # 127-11-3)
 - b. **Repeated Dose Toxicity:** None
 - c. **Reproductive Toxicity:** None
 - d. **Skin Sensitization:** None
 - e. **Phototoxicity/Photoallergenicity:** None
 - f. **Local Respiratory Toxicity:** None
 - g. **Environmental Toxicity:** None
3. **Read-across Justification:** See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

Ethyl pyruvate is reported to occur in the following foods by the VCF*:

- Beer.
- Cheese, various types.
- Cider (apple wine).
- Cocoa.
- Grape brandy.
- Guava wine.
- Honey.
- Mushroom.
- Sake.
- 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.

8. IFRA standard

None.

9. REACH dossier

Available; accessed on 11/15/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, ethyl pyruvate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment

The mutagenic activity of ethyl pyruvate has been evaluated in a bacterial reverse mutation assay conducted similar to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with ethyl pyruvate in dimethyl sulfoxide (DMSO) at concentrations up to 20000 µg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (Andersen and Jensen, 1984). Under the conditions of the study, ethyl pyruvate was not mutagenic in the Ames test. In addition weight of evidence can be made to the hydrolysis product of the target ester; ethyl alcohol (CAS # 64-17-5) and pyruvic acid (CAS # 127-11-3).

There are no studies assessing the clastogenic activity of ethyl pyruvate however, read-across can be made to hydrolysis product of the target material; ethyl alcohol (CAS # 64-17-5) and pyruvic acid (CAS # 127-11-3) (see Section V).

The clastogenic activity of ethyl alcohol was evaluated in several *in vivo* micronucleus tests conducted in compliance or equivalent to GLP regulations and in accordance with OECD TG 474. The test material when administered in water to rats at 4000 mg/kg for 10–30 days or at 7,850 and 15,700 mg/kg for 3 or 7 weeks or to mice at up to 31,400 mg/kg for 27 days, ethanol did not induce a statistically

significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (<https://hpvchemicals.oecd.org/ui/handler.axd?id=2602cc56-d998-4e67-bd78-5454ef3f8f9a> OECD, 2004). In another study, ethanol was administered at > 20 g/kg/day in drinking water to male and female CF-1 mice for 21 days. A positive result was obtained but only at a single very high dose. As the study was conducted over an extend period of time, positive results were not considered relevant (<https://echa.europa.eu/registration-dossier/-/registered-dossier/16105/7/7/3/?documentUUID=e4054254-94c4-4473-bcb8-62977dc6d1cd> ECHA, 2011). In addition, *in vivo* chromosome aberration test was also conducted. No chromosome aberrations were found in the bone marrow or peripheral blood lymphocytes of male Wistar rats given doses of 7,850 and 15,700 mg/kg ethanol in the drinking water for 3 or 6 weeks (<https://hpvchemicals.oecd.org/ui/handler.axd?id=2602cc56-d998-4e67-bd78-5454ef3f8f9a> OECD, 2004).

Based on the available data, ethyl pyruvate does not present a concern for genotoxic potential.

Additional References: Shimizu et al., 1985; Kusakabe et al., 2002; ECHA, 2011.

Literature Search and Risk Assessment Completed On: 01/03/19.

10.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on ethyl pyruvate or on any read-across materials. The total systemic exposure to ethyl pyruvate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment

There are no repeated dose toxicity data on ethyl pyruvate or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to ethyl pyruvate (0.12 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler, 2012) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/07/19.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on ethyl pyruvate or on any

read-across materials. The total systemic exposure to ethyl pyruvate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment

There are no reproductive toxicity data on ethyl pyruvate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to ethyl pyruvate (0.12 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler, 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: 12/17/18.

10.1.4. Skin sensitization

Based on existing data and the application of DST, ethyl pyruvate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment

The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.2). No predictive skin sensitization studies are available for ethyl pyruvate. Acting conservatively, due to the absence of data, the reported exposure was benchmarked utilizing the reactive DST of 64 µg/cm² (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for ethyl pyruvate that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/30/18.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, ethyl pyruvate would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 1

Maximum acceptable concentrations for ethyl pyruvate that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category ^a	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	NRU ^b
2	Products applied to the axillae	0.0015%	NRU ^b
3	Products applied to the face using fingertips	0.029%	NRU ^b
4	Fine fragrance products	0.027%	NRU ^b
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	NRU ^b
6	Products with oral and lip exposure	0.016%	5.7 × 10 ⁻⁴ %
7	Products applied to the hair with some hand contact	0.056%	NRU ^b
8	Products with significant ano-genital exposure	0.0029%	No Data ^c
9	Products with body and hand exposure, primarily rinse-off	0.054%	0.0099%
10	Household care products with mostly hand contact	0.19%	2.9 × 10 ⁻⁴ %
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data ^c
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	NRU ^b

Note.

^a For a description of the categories, refer to the IFRA/RIFM Information Booklet.

^b No reported use.

^c Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

10.1.5.1. Risk assessment

There are no phototoxicity studies available for ethyl pyruvate 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, ethyl pyruvate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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, $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/19/18.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment

There are insufficient inhalation data available on ethyl pyruvate. Based on the Creme RIFM Model, the inhalation exposure is 0.0000064 mg/day. This exposure is 218750.0 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: 12/11/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of ethyl pyruvate 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, ethyl pyruvate was identified as a fragrance material with no potential

to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify ethyl pyruvate 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current VoU (2015), ethyl pyruvate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.2.1.1. *Biodegradation.* No data available.

10.2.2.1.2. *Ecotoxicity.* No data available.

10.2.2.1.3. *Other available data.* Ethyl pyruvate has been pre-registered for REACH with the following available data:

A ready biodegradability study was conducted according to the OECD 301F method, and biodegradation of 97% was observed after 28 days.

A *Daphnia magna* immobilization study was conducted according to the OECD 202 method, and the 48-h LC50 was reported to be 25 mg/L.

An algae inhibition study was conducted according to the OECD 201 method, and the 72-h EC50 (growth rate) was reported to be 2.5 mg/L (ECHA, 2018).

10.2.3. *Risk assessment refinement.* Since ethyl pyruvate 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 $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

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

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	8599			1000000	8.599	

Exposure	Europe (EU)	North America (NA)
Log K _{ow} Used	-0.47	-0.47
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	Not reported	< 1
Risk Characterization: PEC/PNEC	N/A	< 1

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

The RIFM PNEC is 8.599 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level 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: 12/11/18.

11. 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>

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2019.111008>.

Appendix

Read-across Justification

Methods

The read-across analogs were 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 Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster 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).
- 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).

- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <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/opthpv/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/>

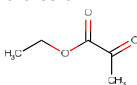
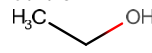
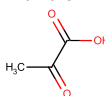
Search keywords: CAS number and/or material names.

*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 05/31/19.

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.

- 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	Read-across Material
Principal Name	Ethyl pyruvate	Ethyl alcohol	Pyruvic acid
CAS No.	617-35-6	64-17-5	127-17-3
Structure			
Similarity (Tanimoto Score)		0.16	0.61
Read-across Endpoint		• Genotoxicity	• Genotoxicity
Molecular Formula	C ₅ H ₈ O ₃	C ₂ H ₆ O	C ₃ H ₄ O ₃
Molecular Weight	116.11	46.06	88.06
Melting Point (°C, EPI Suite)	-50	-114.1	13.8
Boiling Point (°C, EPI Suite)	155	78.2	186.79
Vapor Pressure (Pa @ 25°C, EPI Suite)	423	7.91E+003	1.72E+002
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	-0.47	-0.31	-1.24
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	85082	1e+006	1e+006
J_{max} (µg/cm²/h, SAM)	572.91	7192.05	2053.15
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	9.39E-002	5.07E-001	3.27E-004
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found	• No alert found
Carcinogenicity (ISS)	• No alert found	• No alert found	• No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	• No alert found
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found	• No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	• H-acceptor-path3-H-acceptor	• No alert found	• H-acceptor-path3-H-acceptor
Oncologic Classification	• Not classified	• Not classified	• Not classified
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3

Summary

There are insufficient toxicity data on ethyl pyruvate (CAS # 617-35-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, ethyl alcohol (CAS # 64-17-5) and pyruvic acid (CAS # 127-17-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Read-across alcohol ethyl alcohol (CAS # 64-17-5) and read-across acid pyruvic acid (CAS # 127-17-3) are used as read-across analogs for target ester ethyl pyruvate (CAS # 617-35-6) for the genotoxicity endpoint.
 - The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
 - The read-across materials are major metabolites or analogs of the major metabolites of the target.
 - Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
 - The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
 - According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
 - The target material and the read-across acid have an alert for H-acceptor-path3-H-acceptor. This is due to the 1–4 position of the oxygens in the pyruvic acid branch. The read-across data confirms that the margin of exposure is adequate at current level of use. Therefore, the *in silico* alert is overridden by the data.
 - 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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