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Short Review

RIFM fragrance ingredient safety assessment, ethyl lactate, CAS registry number 97-64-3

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A B S T R A C T

The existing information supports the use of this material as described in this safety assessment. Ethyl lactate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on ethyl lactate show that ethyl lactate is not genotoxic and provided a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory endpoints. Data from ethyl lactate and additional material ethyl (L)-lactate (CAS # 687-47-8) show that there are no safety concerns for ethyl lactate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; ethyl lactate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; ethyl lactate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Version: 062,920. This version replaces any previous versions.
Name: Ethyl lactate

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CAS Registry Number: 97-64-3
Additional CAS Numbers*:
687-47-8 Ethyl (L)-lactate

(*continued on next page*)

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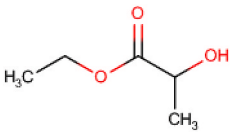
(*continued*)

*Included because the materials are isomers



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
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, 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.

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

Ethyl lactate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on ethyl lactate show that ethyl lactate is not genotoxic and provided a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory endpoints. Data from ethyl lactate and additional material ethyl (L)-lactate (CAS # 687-47-8) show that there are no safety concerns for ethyl lactate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; ethyl lactate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; ethyl lactate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: Ethyl Lactate; ECHA, 2019)
Repeated Dose Toxicity: NOAEL = 51.9 mg/kg/day.	Clary (1998)
Reproductive Toxicity: Developmental toxicity: 75 mg/kg/day. Fertility: 600 mg/kg/day.	(ECHA REACH Dossier: Ethyl Lactate; ECHA, 2019)
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: NOAEC = 200 mg/m^3.	Clary (1998)

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Critical Measured Value: 75% (OECD 301 D) for CAS # 97-64-3	Bowmer (1998)

Bioaccumulation:

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

Ecotoxicity:

Screening-level: Fish LC50: 12,559 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 12,559 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 12.559 µg/L

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

1. Identification

Chemical Name: Ethyl lactate	Chemical Name: Ethyl (L)-lactate
CAS Registry Number: 97-64-3	**CAS Registry Number:** 687-47-8
Synonyms: Ethyl 2-hydroxypropanoate; Ethyl α-hydroxypropionate; Propanoic acid, 2-hydroxy-, ethyl ester; 2-Hydroxypropanoic acid, ethyl ester; Lactic acid, ethyl ester; 乳酸乙; Ethyl lactate	**Synonyms:** Ethyl 2-hydroxypropanoate; Ethyl (L)-lactate
Molecular Formula: $C_5H_{10}O_3$	**Molecular Formula:** $C_5H_{10}O_3$
Molecular Weight: 118.13	**Molecular Weight:** 118.13
RIFM Number: 751	**RIFM Number:** 6549
Stereochemistry: No isomer specified. One stereocenter and 2 total stereoisomers possible.	**Stereochemistry:** L isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

CAS # 97-64-3	CAS # 687-47-8
Boiling Point: 166.19 °C (EPI Suite) **Flash Point:** 47 °C (Globally Harmonized System [GHS]), 117 °F; CC (Fragrance Materials Association [FMA]) **Log K_{OW}:** −0.18 (EPI Suite) **Melting Point:** −27.76 °C (EPI Suite) **Water Solubility:** 472,800 mg/L (EPI Suite) **Specific Gravity:** Not Available **Vapor Pressure:** 0.723 mm Hg @ 20 °C (EPI Suite v4.0), 1.0 mm Hg 20 °C (FMA), 1.08 mm Hg @ 25 °C (EPI Suite) **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$) **Appearance/Organoleptic:** Arctander Volume I 1969: Colorless liquid. Mild, ethereal-buttery odor. Mild, fruity-ethereal, buttery taste in aqueous media.	**Boiling Point:** 166.19 °C (EPI Suite) **Flash Point:** 53 °C (GHS) **Log K_{OW}:** −0.18 (EPI Suite) **Melting Point:** −27.76 °C (EPI Suite) **Water Solubility:** 472,800 mg/L (EPI Suite) **Specific Gravity:** Not Available **Vapor Pressure:** 0.723 mm Hg @ 20 °C (EPI Suite v4.0), 1.08 mm Hg @ 25 °C (EPI Suite) **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$) **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.21% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.00063 mg/kg/day or 0.045 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0081 mg/kg/day (RIFM, 2017)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. *Cramer Classification: class I, low*

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

6.2. *Analogs selected*

a. **Genotoxicity:** None
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

6.3. *Read-across justification*

None.

7. Metabolism

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

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

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

Apple brandy (*Calvados*)
Bourbon whiskey
Cider (Apple wine)
Grape brandy
Malt whiskey
Mezcal (*Agave salmiana*)
Mulberry spirit (*Mouro*)
Nac (French brandy)
Pear brandy
Port wine
Red wine
Rose wine
Sparkling wine
Tequila (*Agave tequilana*)
Whiskey
White wine
Wine

Ethyl (L)-lactate is not reported to occur in foods 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 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

Available for both ethyl lactate (https://echa.europa.eu/registration-dossier/-/registered-dossier/28375 ECHA, 2019) and ethyl (L)-lactate (https://echa.europa.eu/registration-dossier/-/registered-dossier/13866 ECHA, 2011); both accessed 11/15/19.

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, ethyl lactate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 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.

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 (https://echa.europa.eu/registration-dossier/-/registered-dossier/28375/7/7/2/?documentUUID=dd1f1854-7c8a-4376-958d-289c984b82cf 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.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for ethyl lactate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on ethyl lactate.

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, 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, 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).

Therefore, the most conservative NOAEL for systemic toxicity was obtained from the GLP/OECD 412 study and was considered to be 155.6 mg/kg/day, based on decreased bodyweight gain and food consumption at 648.3 mg/kg/day.

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 ethyl lactate, 51.9/0.0081 or 6407.

In addition, the total systemic exposure to ethyl lactate (8.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 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 (accessed 08/21/19).

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

11.1.3. Reproductive toxicity

The MOE for ethyl lactate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. 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 (https://echa.europa.eu/registration-dossier/-/registered-dossier/28375/7/9/2 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 ethyl lactate, 600/0.0081 or 74,074.

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 (https://echa.europa.eu/registration-dossier/-/registered-dossier/28375/7/9/2 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 (https://echa.europa.eu/registration-dossier/-/registered-dossier/28375/7/9/2 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 ethyl lactate, 7.5/0.0081 or 926.

In addition, the total systemic exposure for ethyl lactate (8.1 μg/kg/day) is below the TTC (30 μg/kg/day) for the reproductive toxicity endpoint at the current level of use.

Additional References: None.

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

11.1.4. Skin sensitization

Based on the existing data, ethyl lactate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, ethyl lactate is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Ethyl lactate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and LuSens (https://echa.europa.eu/registration-dossier/-/registered-dossier/28375/7/5/2/?documentUUID=92d7632c-2cdf-4b45-a036-c1c5d61caf77 ECHA, 2019). In a murine local lymph node assay (LLNA), additional material ethyl (L)-lactate was found to be negative up to 100% (https://echa.europa.eu/registration-dossier/-/registered-dossier/13866/7/5/2 ECHA, 2011). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1976).

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

Additional References: Jordan (1971); Marot (1987).

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

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, ethyl lactate 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 ethyl lactate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, ethyl lactate 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/02/19.

11.1.6. Local respiratory toxicity

The MOE for ethyl lactate is adequate for the local respiratory toxicity endpoint at the current level of use.

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. Five rats/sex/treatment group (strain unknown) were exposed to ethyl lactate vapors for 6 h/day, 5 days/week for 28 days in 2 separate studies conducted in accordance with OECD 412 guidelines in compliance with GLP (Clary, 1998). One study used exposure levels of 0, 150, 600, and 2500 mg/m^3, and another study used exposure levels of 0, 25, 75, and 200 mg/m^3. Body weight, food consumption, hematological, biochemical, organ weight, and gross and microscopic evaluations were carried out. No treatment-related effects were observed following ethyl lactate exposures up to 600 mg/m^3. Degenerative changes of the nasal olfactory epithelium and hyperplasia of the respiratory epithelium and of the goblet cells were observed at 600 mg/m^3 and higher. Therefore, the NOAEC for local respiratory effects was identified as 200 mg/m^3 from the second study.

This NOAEC expressed in mg/kg lung weight/day is:

- (200 mg/m^3) × (1 m^3/1000 L) = 0.2 mg/L
- MV of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.2 mg/L) × (61.2 L/d) = 12.24 mg/day
- (12.24 mg/day)/(0.0016 kg lung weight of rat*) = 7650 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.045 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015; Safford, 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.069 mg/kg lung weight/day resulting in a MOE of 110,870 (i.e., [7650 mg/kg lung weight/day]/[0.069 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.045 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: “Comparative Physiology and Anatomy,” subsection, “Comparative Airway Anatomy.”

Additional References: None.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	12559			1000000	12.559	

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl lactate was performed following the RIFM Environmental Framework (Salvito, 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 lactate 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 lactate 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, 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.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), ethyl lactate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. For CAS # 97-64-3.

Bowmer (1998): The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 75% was observed after 28 days.

11.2.1.2.2. Ecotoxicity. For CAS # 97-64-3.

Bowmer (1998): The acute fish (*Danio rerio*) toxicity test was conducted according to the OECD 203 guidelines under semi-static conditions. The 96-h LC50 value based on nominal concentrations was reported to be 320 mg/L (95% CI: 305–417 mg/L).

Bowmer (1998): The *Daphnia* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on nominal concentration was reported to be 683 mg/L (95% CI: 592–788 mg/L).

Bowmer (1998): The algae growth inhibition test was conducted according to the OECD 201 guidelines under semi-static conditions. The 96-h EC50 values based on nominal concentrations for growth rate and yield were reported to be 3500 mg/L and 2300 mg/L, respectively.

11.2.1.2.3. Other available data. Ethyl lactate has been registered for REACH with following additional information available at this time:

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301 F guideline. Biodegradation of 70% was observed after 28 days (ECHA, 2019).

11.2.2. Risk assessment refinement

Since ethyl lactate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	−0.18	−0.18
Biodegradation Factor Used	0	0
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 12.559 μg/L. The revised PEC/PNECs for EU and NA (No VoU) are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

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

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.

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