LACTIDE

(CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: August 5, 2020

Expiration Date: August 5, 2025

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GreenScreen® Executive Summary for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)

Lactide is a chemical that functions as a pH regulator in food, a swelling agent in bakery products, a bacteriostat in meat emulsions, a reagent for chemical reactions that do not produce water molecules, a destabilizer for production of porous ceramics, and an electrolyte in lithium batteries. It is a non-flammable, non-volatile, water soluble solid that exist as white flakes under standard temperature and pressure. Lactide rapidly hydrolyzes in water to form lactic acid.

Lactide was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement"). This score is based on the following hazard score combinations:

- Benchmark 3c
  - Moderate Group II Human Health Hazard (single dose neurotoxicity-Ns)
  - High Group II Human Health Hazard (eye irritation-IrE)

The previous publicly available version of this GreenScreen® assessment (version 1.2, dated October 22, 2013) assigned a GreenScreen Benchmark™ Score of 2 ("Use but Search for Safer Substitutes") primarily due to assigning a Very High score for eye irritation due to relying on data on the surrogate lactic acid for this endpoint. Since then, eye irritation data for lactide have become available and are included in the present assessment, which result in a lower score (i.e., High) for eye irritation. Similarly, the score for skin irritation is reduced from High to Low. Additionally, the scores for acute aquatic toxicity-AA and chronic aquatic toxicity-CA are reduced from Moderate to Low, and for persistence changed from Moderate to Low, due to using data on the hydrolysis product lactic acid rather than modeling to evaluate these endpoints. The revised GreenScreen Benchmark™ Score of 3 reflects the currently available data on the target chemical and surrogates.

GreenScreen® Hazard Summary Table for Lactide

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeat*	single	repeat*										
L	**L**	*L*	*L*	*L*	**L**	**L**	**L**	*M*	*L*	**L**	*L*	**L**	*H*	**L**	*L*	**L**	**vL**	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Chemical Assessment for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)

Method Version: GreenScreen® Version 1.4
Assessment Type[1]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.2) Prepared By:
Name: Kristen Schaefer, M.F.S.
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Organization: ToxServices LLC
Date: March 1, 2013

Quality Control Performed By:
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Organization: ToxServices LLC
Date: March 11, 2013

GreenScreen® Assessment (v.1.2) Updated By:
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Title: Toxicologist
Organization: ToxServices LLC
Date: October 14, 2013

Update Quality Control Performed By:
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Organization: ToxServices LLC
Date: October 15, 2013

GreenScreen® Assessment (v.1.4) Updated By:
Name: Rachel Galante, M.P.H.
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Organization: ToxServices LLC
Date: May 9, 2018

Update Quality Control Performed By:
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Title: Senior Toxicologist
Organization: ToxServices LLC
Date: May 22, 2018

GreenScreen® Assessment (v.1.4) Updated By:
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Organization: ToxServices LLC
Date: July 10, 2020, August 5, 2020

Update Quality Control Performed By:
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Title: Senior Toxicologist
Organization: ToxServices LLC
Date: July 13, 2020, August 5, 2020

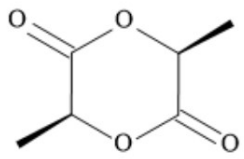
Expiration Date: August 5, 2025[2]

Chemical Name: Lactide

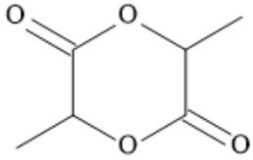
CAS Number: 4511-42-6; 615-95-2; 95-96-5; 13076-17-0

Chemical Structure(s):
The CAS #4511-42-6 refers to the sterioisomer L-lactide, while the CAS numbers 615-95-2 and 95-96-5 refer to the substance with no sterioisomer designation (i.e., DL-lactide), although CAS #95-96-5 appears to be the primary CAS number based on the ChemIDplus entry for this chemical. CAS #13076-17-0 refers to the D-lactide isomer. This document presents an assessment the DL-lactide mixture and individual isomers.

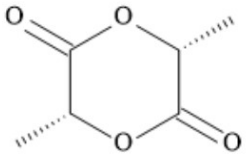
[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).



L-Lactide
(CAS #4511-42-6)



DL-Lactide
(CAS #615-95-2; 95-96-5)



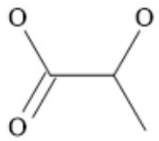
D-Lactide
(CAS #13076-17-0)

Also called:
L-Lactide (CAS #4511-42-6)
Lactide, L-; EC 224-832-0; (3S-cis)-3,6-Dimethyl-1,4-dioxane-2,5-dione; 1,4-Dioxane-2,5-dione, 3,6-dimethyl-, (3S,6S)- (ChemIDplus 2020a)

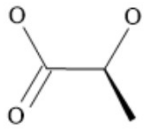
DL-Lactide (CAS #615-95-2; 95-96-5)
Dilactide; 3,6-Dimethyl-1,4-dioxane-2,5-dione; 3,6-Dimethyl-2,5-dioxo-1,4-dioxane; EC 202-468-3; Lactic acid, bimol. cyclic ester; Lactide; Propanoic acid, 2-hydroxy-, bimol. cyclic ester; 1,4-Dioxane-2,5-dione, 3,6-dimethyl-; p-Dioxane-2,5-dione, 3,6-dimethyl- (8CI) (ChemIDplus 2020b)

D-Lactide (CAS #13076-17-0)
Lactide, D-; EC 603-436-5; (3R,6R)-3,6-Dimethyl-1,4-dioxane-2,5-dione; 1,4-Dioxane-2,5-dione, 3,6-dimethyl-, (3R,6R)- (ChemIDplus 2020c)

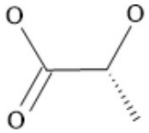
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Limited data were identified for lactide. In order to address data gaps, ToxServices evaluated toxicity data for chemical surrogates. Lactide is the cyclic diester of lactic acid and both chemicals have carbonyl groups as their major functional groups, with lactic acid having a carboxylic acid and ketone group and lactide having two ester groups. Furthermore, lactide is expected to form lactic acid in the presence of water (Futerro 2009). Lactide and lactic acid are expected to have similar chemistry, so ToxServices used lactic acid as a surrogate to address the data gaps for lactide. In addition, when no data were identified for lactide or lactic acid, ToxServices used data for calcium lactate (i.e., the calcium salt of lactic acid) to fill the data gaps. The calcium ion is ubiquitous and tightly controlled in cells, and therefore not expected to exert additional toxicity.



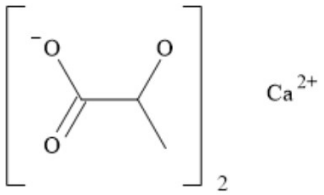
Lactic Acid
(CAS #50-21-5)



L-Lactic Acid
(CAS#79-33-4)



D-Lactic Acid
(CAS #10326-41-7)



Calcium Lactate (CAS #814-80-2)

Identify Applications/Functional Uses (Futerro 2020)**:**
1. pH regulator in food
2. Swelling agent in bakery products
3. Bacteriostat in meat emulsions
4. Reagent for chemical reactions that do not produce water molecules (transesterification, amidation, ring opening polymerization, etc.)
5. Destabilizer for production of porous ceramics
6. Electrolyte in lithium batteries

Known Impurities[3]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for Lactide[4,5,6]: Lactide was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 3c
  - Moderate Group II Human Health Hazard (single dose neurotoxicity-Ns)
  - High Group II Human Health Hazard (eye irritation-IrE)

Figure 1: GreenScreen® Hazard Summary Table for Lactide

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeat*	single	repeat*										
L	**L**	*L*	*L*	*L*	**L**	**L**	**L**	*M*	*L*	**L**	*L*	**L**	*H*	**L**	*L*	**L**	**vL**	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

Environmental Transformation Products

Lactide hydrolyzes rapidly in water to form lactic acid (CAS #50-21-5) (ECHA 2020a,b). In order to identify additional transformation products, ToxServices predicted the hydrolysis products under acidic, neutral, and basic pH using OECD QSAR Toolbox (OECD 2020). Using this approach, ToxServices identified DL-lactic acid lactate (CAS #617-57-2), also known as lactic acid dimer, and lactic acid as hydrolysis products of lactide under acidic and basic conditions. No hydrolysis products are predicted for lactide under neutral pH. Normal rain has a pH of ~5.6[7] and surface waters are slightly acidic as a result of rainfall runoff. Therefore, ToxServices considered both DL-lactic acid lactate and lactic acid

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.
[7] https://www.epa.gov/acidrain/what-acid-rain

as feasible and relevant transformation products for lactide. As neither chemical is an LT-1 or Benchmark 1 chemical, ToxServices did not adjust the Benchmark Score for lactide based on transformation products.

Table 1: Environmental Transformation Product Summary

Life Cycle Stage	Transformation Pathway	Environmental Transformation Product	CAS #	Feasible (Yes or No)	Relevant (Yes or No)	GreenScreen® List Translator Score or GreenScreen® Benchmark™ Score[8,9]
In use, end-of-life	Hydrolysis (acidic and basic)	DL-Lactic acid lactate	617-57-2	Yes	Yes	Not listed in Pharos database
In use, end-of-life	Hydrolysis (acidic and basic)	Lactic acid	50-21-5	Yes	Yes	LT-UNK

Introduction

Lactide is the monomer used to synthesize polylactic acid, a biocompatible and biodegradable plastic (Futerro 2020). Lactide is produced by the oligomerization of lactic acid followed by cyclization. Lactide has two stereoisomer forms: L-lactide (CAS #45411-42-6) and D-lactide (CAS #13076-17-0). CAS #615-95-2 refers to a substance with no sterioisome designation (i.e., DL-lactide), and is also associated with the CAS #95-96-5.

ToxServices assessed lactide against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List (SCIL)

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2020a). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

L-Lactide (CAS #4511-42-6), DL-lactide (CAS #615-95-2; 95-96-5), and D-Lactide (CAS #13076-17-0) are not listed on the SCP SCIL. However, the surrogates DL-lactic acid (CAS #50-21-5) and L-lactic acid (CAS #79-33-4) are listed on the SCP SCIL as acceptable preservatives and antioxidants and processing aids and additives. The surrogate L-lactic acid is also listed as an acceptable antimicrobial additive and chelating agent.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2020) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[10] which are not considered GreenScreen® Specified Lists but are additional information

[8] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2020) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[9] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).
[10] DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for lactide can be found in Appendix C.

- Lactide is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Lactide is not listed on the U.S. DOT list.
- Lactide is on the following list for multiple endpoints:
  - German FEA - Substances Hazardous to Waters - Class 1 - Low Hazard to Waters
- Lactide is not present on any GreenScreen®-specified lists for single endpoints.

Hazard Statement and Occupational Control

Harmonized EU GHS classifications are not available for lactide. The REACH registration dossier authors have self-classified DL-lactide, L-lactide, and D-lactide as a GHS Category 2 eye irritant (H319) (ECHA 2020a,b,c).

Table 2: H Statements for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0) (ECHA 2020a,b,c)

H Statement	H Statement Details
H319	Causes serious eye irritation

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Safety glasses with side-shields, gloves, impervious clothing, respiratory (for nuisance exposures)	Sigma-Aldrich 2020a,b	None established	Sigma-Aldrich 2020a,b

Physicochemical Properties of Lactide

Lactide is a which flaky solid under standard temperature and pressure. It is predicted to have a low vapor pressure (0.00233 mm Hg), indicating that it exists mostly in the solid phase. It is very soluble in water, and is slightly more soluble in octanol than in water (log K_{ow} = 0.4). Its log K_{ow} indicates it is not expected to bioaccumulate in biota due to its low lipophilicity.

Table 4: Physical and Chemical Properties of Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)

Property	Value	Reference
Molecular formula	$C_6H_8O_4$	ChemIDplus 2020a,b,c
SMILES Notation	C[C@@H]1OC(=O)[C@H](C)OC1=O (L-Lactide) C1([C@@H](OC(=O)[C@@H](O1)C)C)=O (DL-Lactide) C[C@H]1OC(=O)[C@@H](C)OC1=O (D-Lactide)	ChemIDplus 2020a ChemIDplus 2020b ChemIDplus 2020c
Molecular weight	144.125	ChemIDplus 2020a,b,c
Physical state	Solid	ECHA 2020a,b
Appearance	White flakes	ECHA 2020a,b
Melting point	97°C (OECD Guideline 102)	ECHA 2020a,b

Table 4: Physical and Chemical Properties of Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)		
Property	**Value**	**Reference**
Boiling point	266°C (OECD Guideline 103)	ECHA 2020a,b
Vapor pressure	0.311 Pa (0.00233 mm Hg) at 25°C (estimated)	ECHA 2020a,b
Water solubility	16.7 g/L at 20°C (OECD Guideline 105)	ECHA 2020a,b
Dissociation constant	Not applicable	ECHA 2020a,b
Density/specific gravity	1.33 g/cm^3 at 20°C (OECD Guideline 109)	ECHA 2020a,b
Partition coefficient	Log K_{ow} = 0.4 at 25°C (neutral pH) (OECD Guideline 117)	ECHA 2020a,b

Toxicokinetics

Limited toxicokinetics data are available. The surrogate lactic acid is absorbed by the skin at the rate 25% in an *in vitro* study. Absorbed lactide is rapidly hydrolyzed to lactic acid which may be utilized in energy metabolism. No other data are identified.

- ECHA 2020a,b
  - Lactide has a half-life of three hours in aqueous media and will rapidly hydrolyze in the stomach following ingestion. The half-life in 0.1 N hydrochloric acid is 0.4 hours at 37°C. Therefore, systemic exposure of ingested lactide is in the form of lactic acid (Klimisch Score 2, reliable with restrictions).
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: A non-GLP-compliant *in vitro* dermal absorption study was performed with pig skin exposed to 2 or 75 µL ^{14}C-radiolabeled L-lactic acid (150 mCi/mmol) in oil-in-water (o/w), water-in-oil (w/o), and water-in-oil-in water (w/o/w) emulsions under occlusive dressing for six hours. For the 2 µL volume, the levels of radioactivity in the stratum corneum, epidermis, dermis, and receptor fluid were 16%, 2%, 4%, and 0.5%, respectively. In total up to 25% of the lactic acid penetrated into or through the skin after the six-hour exposure period. The "total tissue delivery" for lactic acid was ranked as o/w > w/o/w > w/o for the three emulsions (Klimisch Score 2, reliable with restrictions).
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: Lactic acid is the endogenous product of anoxic (without oxygen) metabolism via glycolysis. Some lactic acid may be excreted or reabsorbed and converted back to pyruvate or glucose for continued energy metabolism (Klimisch score 4, not assignable).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): L

Lactide was assigned a score of Low for carcinogenicity based on the lack of carcinogenic potential identified for the surrogates calcium lactate and lactic acid. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on strong surrogates.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.

- ECHA 2020a,b
    - *Surrogate: Calcium Lactate (CAS #814-80-2):* In a two-year carcinogenicity study conducted in a manner similar to OECD Guideline 451 (GLP status unknown), F344 rats (50/dose/sex) received calcium lactate (>97% purity) in drinking water *ad libitum* at concentrations of 2.5 or 5% (equivalent to total doses of 329.4 and 625.4 g for males and 237.7 and 412.1 g for females, respectively). A nine-week treatment-free period followed the treatment period. Body weight, water consumption, clinical signs, mortality, hematology, clinical chemistry, organ weights, gross pathology and histopathology were evaluated. Treatment did not produce statistically significant, dose-related increases in tumor incidences in any organ or tissue. The authors concluded that calcium lactate was not carcinogenic under the tested conditions (Klimisch Score 2, reliable with restrictions).
    - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: In a 5-13-month study in female rabbits (5/group in the 13-month study, number not specified for the five month study), animals received L-lactic acid in drinking water given twice daily at the doses of 100 to 200 mg/kg/day (5 months) or 100 to 700 mg/kg/day (13 months). No tumors were reported after 5 or 16 months. No additional details were provided (Klimisch Score 2, reliable with restrictions in ECHA 2020a, and Klimisch Score 4, not assignable in ECHA 2020b).

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

Lactide was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity for the surrogate lactic acid in a battery of *in vitro* assays. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on a strong surrogate.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a,b
    - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4): In vitro*: L-Lactic acid was negative for mutagenicity in a GLP-compliant bacterial reverse mutation assay conducted according to OECD Guideline 471/EU Method B.13/14. *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP_2 *uvr*A were exposed to lactic acid (90% purity) in water at 3-5,000 µg/plate with and without exogenous metabolic activation (unspecified S9 mix). 4-Nitroquinoline-N-oxide, 2-nitrofluorene, sodium azide, methylmethanesulfonate, ICR-191, and 2-aminoanthracene were the positive controls. Treatment did not increase the mutation frequency in the presence or absence of metabolic activation. The vehicle and positive controls were valid (Klimisch Score 2, reliable with restrictions).
    - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4): In vitro*: Lactic acid was negative for mutagenicity in an Ames reverse mutation assay conducted in a manner similar to OECD Guideline 471 (GLP status not specified). *S. typhimurium* tester strains TA97, TA98, TA100, and TA104 were exposed to lactic acid (purity not specified) in medium/water at 0.5, 1, or 2 µL/plate with and without exogenous metabolic activation (rat liver homogenate S9). 2-Aminoanthracene served as the positive control. Treatment did not increase the mutation frequency in the presence or absence of metabolic activation. The

untreated negative and positive controls were valid (Klimisch Score 2, reliable with restrictions).

- *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4):* *In vitro*: Lactic acid was negative for mutagenicity in a non-GLP-compliant Ames reverse mutation assay conducted in a manner similar to OECD Guideline 471. *S. typhimurium* tester strains TA92, TA94, TA98, TA100, TA1535, TA1537, and TA2637 were exposed to lactic acid (90.5% aqueous solution) in water/phosphate buffer ≤ 10 mg/plate with and without exogenous metabolic activation (rat liver homogenate S9). No positive controls were included in the study design. Treatment did not increase the mutation frequency in the presence of absence of metabolic activation. No data were provided for untreated negative or vehicle controls (Klimisch Score 2, reliable with restrictions).
- *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4):* *In vitro*: Lactic acid was negative for mutagenicity in a pre-GLP bacterial reverse mutation assay conducted in a manner similar to OECD Guideline 471. *E. coli* strain B/Sd-4/1,3,4,5 and B/Sd-4/3,4 at concentrations of 0.01-0.02% without exogenous metabolic activation. No positive controls were included in the study design. Treatment did not increase the mutation frequency in the presence of absence of metabolic activation. No data were provided for untreated negative or vehicle controls (Klimisch Score 2, reliable with restrictions).
- *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4):* *In vitro*: L-Lactic acid was negative for mutagenicity in a GLP-compliant mammalian cell gene mutation assay conducted according to OECD Guideline 476/EU Method B.17. Mouse lymphoma L5178Y TK+/- cells were exposed to lactic acid (90% purity) in RPMI 1640 medium at 0.54-901 µg/mL with and without exogenous metabolic activation (unspecified S9 mix). Cyclophosphamide and methylmethanesulfonate were the positive controls. Treatment in the presence or absence of metabolic activation did not increase the mutation frequency. The vehicle, untreated negative, and positive controls were valid (Klimisch Score 2, reliable with restrictions).
- *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4):* *In vitro*: L-Lactic acid was negative for clastogenicity in a GLP-compliant *in vitro* chromosome aberration assay conducted according to OECD Guideline 473/EU Method B.10. Peripheral human lymphocytes were exposed to lactic acid (90% purity) in RPMI 1640 medium at 10-901 µg/mL with and without exogenous metabolic activation (unspecified S9 mix). Cyclophosphamide and mitomycin C were the positive controls. Treatment in the presence or absence of metabolic activation did not increase the frequency of chromosomal aberrations. The vehicle, untreated negative, and positive controls were valid (Klimisch Score 2, reliable with restrictions).
- *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4):* *In vitro*: Lactic acid was negative for clastogenicity in a non-GLP-compliant *in vitro* chromosome aberration assay conducted in a manner similar to OECD Guideline 473. Chinese hamster ovary (CHO) cells were exposed to lactic acid (90% aqueous solution, vehicle not specified) at 8-35 mM with and without exogenous metabolic activation (rat liver homogenate S9). Positive controls were not included in the study design. Treatment did not increase the frequency of chromosomal aberrations with or without metabolic activation when the test solutions were neutralized to pH 6.4. Pseudo-positive reactions were identified at non-physiological low pH. No data were provided for vehicle or untreated negative controls (Klimisch Score 2, reliable with restrictions).
- *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4):* *In vitro*: Lactic acid was negative for clastogenicity in an *in vitro* chromosome aberration assay conducted in a manner similar to OECD Guideline 473 (GLP status not specified). Chinese hamster lung

fibroblast cells were exposed to lactic acid (90.5% aqueous solution) in water/saline at ≤ 1 mg/mL with and without exogenous metabolic activation (rat liver homogenate S9). No positive controls were included in the study design. Treatment did not increase the frequency of chromosome aberrations in the presence or absence of metabolic activation. No data were provided for untreated negative or vehicle controls (Klimisch Score 2, reliable with restrictions).

- U.S. EPA 2008, NTP 2020
    - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4): In vitro:* Lactic acid was negative for mutagenicity in a bacterial reverse mutation assay conducted by the National Toxicology Program (NTP). *S. typhimurium* tester strains TA97, TA98, TA100 and TA1535 were exposed to lactic acid (purity not specified) in water at ≤ 10,000 µg/plate in the presence and absence of exogenous metabolic activation (hamster or rat S9). 2-Aminoanthracene, sodium azide, 9-aminoacridine, and 4-nitro-O-phenylenediamine were used as positive controls. Treatment did not increase the mutation frequency in the presence of absence of metabolic activation. The solvent and positive controls performed as expected.

Reproductive Toxicity (R) Score (H, M, or L): *L*

Lactide was assigned a score of Low for reproductive toxicity based on limited negative data in rats and U.S. Environmental Protection Agency (U.S. EPA)'s expert judgment as well as SCIL listing on the surrogate lactic acid. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low due to the lack of details available for the identified study and as it is based on expert judgement.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020d
    - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: In a dietary study, rats (strain, sex or number not specified) were fed stock diet supplemented with 0, 2.5 or 5% lactic acid prior to breeding and through pregnancy to parturition. The sex ratio of the offspring was not affected by the treatment. No further information was provided (Klimisch Score 4, not assignable).
        - Changes in sex ratio can be viewed as either a reproductive or developmental toxicity endpoint depending on when the parental exposures occurred. Since the exposures were initiated prior to breeding and continued until birth, it is not clear if effects on sex ratio, or lack of effects in the case of lactic acid, should be classified under reproductive or developmental toxicity. Mechanistic data explaining changes in sex ratio following chemical exposure suggest that effects on sex ratio may be due to differential fertilization capacity between X chromosome-bearing and Y chromosome-bearing sperm (Ishihara et al. 2010). Therefore, ToxServices considers effects on sex ratio to be an aspect of reproductive toxicity and concludes that this should be classified under reproductive toxicity and not developmental toxicity.
- No data were identified for lactide and limited data are available for lactic acid. However, reproductive toxicity testing for lactic acid "is not deemed necessary because [it] is a normal component of human intermediary metabolism" (U.S. EPA 2008). In addition, lactic is present on the SCIL, suggesting a low reproductive toxicity concern. Based on limited available data and expert judgment, the reproductive toxicity potential of lactide is low.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Lactide was assigned a score of Low for developmental toxicity based on the lack of overt, treatment-related effects on development in a mouse study and U.S. EPA's expert opinion as well as the SCIL listing for the surrogate lactic acid. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low due to the low level of detail available for the critical study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020d
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: Pregnant female Swiss mice (number not specified) were administered gavage doses of lactic acid (purity not specified) at 0 or 570 mg/kg/day on gestation days 6-15. Treatment slightly but not statistically significantly decreased fetal weights and produced a statistically significant delay in parietal bone ossification. However, the authors argue that the delayed ossification may be a consequence of the decreased fetal weight and, therefore, did not consider this effect to be test item-specific. Treatment did not produce maternal toxicity (specific endpoints not identified but likely constituted maternal body weight, food consumption, and clinical signs of toxicity). No further details were provided. ToxServices identified maternal and development NOAELs of 570 mg/kg/day for this study (Klimisch Score 4, not assignable).
- U.S. EPA 2008
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: Testing for developmental toxicity is not deemed necessary because the substance is a normal component of human intermediary metabolism.

Endocrine Activity (E) Score (H, M, or L): *L*
Lactide was assigned a score of Low for endocrine activity based on the weight of evidence indicating that lactide does not bind to the estrogen, androgen, or thyroid receptors and the expert opinion by the U.S. EPA that states the metabolite lactic acid is not likely to be endocrine active. GreenScreen® criteria classify chemicals as a Low hazard for endocrine activity when adequate and negative studies are available for estrogen, antiestrogen, androgen, antiandrogen, and thyroid activities (CPA 2018b). The confidence in the score is low as no measured data for estrogen, androgen, or thyroid hormones are identified.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2020b
  - Lactide (CAS #95-96-5) was active in 2/18 estrogen receptor (ER) assays, 0/12 androgen receptor (AR) assays, 0/2 steroidogenesis assays, and 0/8 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century.
- U.S. EPA 2009
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: As part of a weight of evidence analysis, the U.S. EPA concluded that there is no evidence that a metabolite of lactic acid acts in an endocrine-disrupting manner. As lactic acid is naturally occurring in

plants and animals and is a component of cellular energy production, the U.S. EPA expects no adverse effects to the endocrine system to result from exposures to lactic acid.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): L

Lactide was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} s > 2,000 mg/kg for lactide and a four-hour aerosol LC_{50} > 7.94 mg/L for the surrogate lactic acid. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50}s are > 2,000 mg/kg and four-hour aerosol LC_{50} values are > 5 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - *Oral:* LD_{50} (male and female Crl:(WI) WU BR rats) > 2,000 mg/kg (GLP-compliant, OECD Guideline 423/EU Method B.1) (Klimisch Score 1, reliable without restriction).
    - Performed with L-lactide (CAS #4511-42-6).
  - *Dermal:* LD_{50} (male and female Wistar rat) > 2,000 mg/kg (GLP-compliant, OECD Guideline 402/EU Method B.3/EPA OPPTS 870.1200) (Klimisch Score 1, reliable without restriction).
- ECHA 2020a; U.S. EPA 2008
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4): Inhalation:* four-hour nose-only aerosol LC_{50} (male and female Fisher 344 rats) >7.94 mg/L (GLP-compliant, OECD Guideline 403) (Klimisch Score 2, reliable with restrictions).
- ChemIDplus 2020b
  - *Oral:* LD_{50} (rat, sex and strain not reported) > 5,000 mg/kg
    - Performed with DL-lactide (CAS #615-95-2; 95-96-5).
  - *Dermal:* LD_{50} (rabbit, sex and strain not reported) >2,000 mg/kg
    - Performed with DL-lactide (CAS #615-95-2; 95-96-5).

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score (vH, H, M, or L): L

Lactide was assigned a score of Low for systemic toxicity (single dose) based on the lack of systemic toxicity produced following single oral or dermal doses of lactide or single inhalation exposures to the surrogate lactic acid. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - *Oral:* In a GLP-compliant acute oral toxicity study according to OECD Guideline 423, male and female Crl:(WI) WU BR rats (3/sex/dose) were administered gavage doses of L-lactide (>99.5% purity) in corn oil at 2,000 mg/kg. Treatment did not produce mortalities, clinical

sings of toxicity, changes to body weight, or gross alterations detected at necropsy (Klimisch Score 1, reliable without restriction).
    - *Dermal:* In a GLP-compliant acute dermal toxicity study according to OECD Guideline 402, male and female Wistar rats (5/sex/dose) were administered topical applications of L-lactide (99% purity) in polyethylene glycol at a dose of 2,000 mg/kg under occlusive conditions for 24 hours. Treatment did not produce mortalities, clinical sings of toxicity, changes to body weight, or significant gross alterations detected at necropsy (Klimisch Score 1, reliable without restriction).
- ECHA 2020a; U.S. EPA 2008
    - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4): Inhalation:* In a GLP-compliant acute inhalation toxicity study according to OECD Guideline 403, male and female Fischer 344 rats (5/sex/dose) were exposed nose-only to L-lactic acid aerosol (80-85% purity) at 7.94 mg/L for four hours and then observed for 14 days. Rapid breathing and lacrimation were observed in the treated animals. One and 3 hours after exposure, all the animals displayed hunched posture and red stained fur around the eyes (tearing), ruffled fur and appeared ungroomed with soiled fur. Female rats appeared lethargic at 1 (2/5) and 3 (5/5) hours of exposure. The 2 females that were lethargic after 1-hour exposure had rapid, shallow breathing and appeared to be gasping briefly following exposure. Most animals appeared to have recovered from lethargy and unkempt fur by 24 hours. 4/5 females had ruffled and ungroomed fur until post-treatment day 4. One female died on day 8 and another had rapid, shallow breathing and slight tremors on day 5 post-treatment. Treatment did not adversely affect body weights or produce gross lesions as identified at necropsy (Klimisch Score 2, reliable with restrictions).

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score (H, M, or L): L

Lactide was assigned a score of Low for systemic toxicity (repeated dose) based on the lack of systemic toxicity in subchronic oral toxicity tests of L-lactide and the surrogate calcium lactate at doses ≤ 100 mg/kg/day. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a,b; Hébert et al. 1999
    - *Oral:* A subchronic repeated oral dose toxicity study conducted in a manner similar to OECD Guideline 409 (GLP status not specified) was performed with beagle dogs (4/sex/dose) administered oral gelatin capsules containing L-lactide [18:1 mixture of L-lactide and m-lactide (CAS #13076-19-2)] at 0, 4, 20 or 100 mg/kg/day for 13 weeks. Evaluations included clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology. Treatment did not affect survival, body weights, food consumption, hematology, clinical chemistry, or urinalysis parameters, or organ weights. One female in the control and high dose groups exhibited emesis (vomiting) during week 9, and one high dose female exhibited bloody diarrhea during week 6. Treatment produced a stomach foci in one low dose female and one male and female each in the high dose group and mode. Histopathological evaluation identified moderately severe ulceration of the stomach mucosa in one high dose female. The authors concluded that the pathological changes identified in the stomach were

likely a consequence of the irritating properties of the test substance. Based on the lack of systemic effects, the authors identified a systemic toxicity NOAEL of 100 mg/kg/day (Klimisch Score 2, reliable with restrictions).

- *Oral:* A two-week repeated oral dose toxicity study conducted in a manner similar to OECD Guideline 407 was performed with beagle dogs (2/sex/dose) administered oral gelatin capsules containing L-lactide [18:1 mixture of L-lactide and m-lactide (CAS #13076-19-2)] at 0, 10, 100, 400, 1,000, or 2,500 mg/kg/day for 14 days. Evaluations included clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology. Treatment did not negatively affect survival or hematology, clinical chemistry, or urinalysis parameters. Clinical signs consistent with irritation of the alimentary tract were detected in dogs in the 1,000 and 2,500 mg/kg/day dose groups. Animals in the high dose group also exhibited reduced body weight gain and absolute and relative thymus weights, and high dose animals exhibited reduced absolute and relative spleen weights. The authors considered these effects to be secondary to the stress resulting from irritation of the gastrointestinal tract. Gross and microscopic lesions were indicative of irritation, and included dark foci and hemorrhage of the stomach lining, as well as erosion and ulceration of the stomach and the esophagus. All of the high-dose dogs also exhibited renal tubular regeneration, which may indicate repair of previous necrosis of the tubular epithelium. No further details were provided. The authors identified a systemic toxicity NOAEL and LOAEL of 1,000 and 2,500 mg/kg/day, respectively (Klimisch Score 2, reliable with restrictions).

- ECHA 2020a,b; U.S. EPA 2008
  - <u>*Surrogate: Calcium Lactate (CAS #814-80-2)*</u>: *Oral*: In a 13-week oral toxicity study, F344 rats (5/sex/dose) received calcium lactate via drinking water at 0, 0.3, 0.6, 1.25, 2.5 and 5% (reported in U.S. EPA (2008) as equivalent to approximately 0, 30, 60, 125, and 500 mg/kg/day, respectively. However, these dose levels do not appear correct and ToxServices calculated the equivalent doses as 0, 488, 975, 2,032, 4,063, and 8,125 mg/kg/day lactic acid, respectively[11]). A less than 10% decrease in body weight gain was noted in all dose groups compared to control. Changes in some hematological and biochemical parameters were observed while no severe toxicological findings were found upon histopathological examination. In another study, F344 rats (10/sex) were provided a synthetic diet containing calcium lactate at 0, 5, 10, 20, or 30% (equivalent to calcium lactate doses of 0, 5,235, 10,470, 20,940, and 32,310 mg/kg/day, respectively)[12] for 20 weeks. Some animals (5/sex/dose) were necropsied in the 8th week while the remaining rats were sacrificed in the 20th week. Body weight gain was decreased in the highest dose group. Histological examination revealed nephrocalcinosis in all groups including the control group, but the degree of occurrence was dose-dependent and females had worse symptoms than males. In a follow-up study, male F344 rats (10/group) were given either the base diet or synthetic diet (no calcium lactate in either diet) for 8 weeks. Five rats from each group were sacrificed in the 4th week while the remaining rats were sacrificed in the 8th week. Nephrocalcinosis was found only in the group given synthetic diet. The authors concluded that nephrocalcinosis was dependent on the low Ca/P ratio (<1) of the synthetic diet. A NOAEL of 8,125 mg/kg/day was established based on the absence of effects at the highest dose

[11] According to U.S. EPA (1988), water factors for F344 rats in subchronic studies are 0.156 and 0.169 kg/kg/day for males and females, respectively, giving rise to an average of 0.1625 L/kg/day. 5% in drinking water is therefore equivalent to 50,000 mg/L x 0.1625 L/kg/day = 8,125 mg/kg/day. =

[12] According to U.S. EPA (1988), food factors for F344 rats in subchronic studies are 0.100 and 0.113 kg/kg/day in males and females, respectively, giving rise to an average food factor of (0.100 + 0.113)/2 = 0.1065 kg/kg/day. Thus, 5% calcium lactate in the diet is equivalent to 5% x 0.1065 kg/kg/day x 1,000,000 mg/kg = 5,325 mg/kg/day calcium lactate.

tested in the initial study, and a LOAEL of 5,235 mg/kg/day for nephrocalcinosis was observed in the 2nd study (Klimisch Score 4, not assignable).

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *M*
Lactide was assigned a score of Moderate for neurotoxicity (single dose) based on ToxServices classifying it as a Category 3 specific target organ toxicant following single exposures for narcotic effects under GHS criteria. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when they are classified as GHS Category 3 specific target organ toxicant following single exposures for narcotic effects (CPA 2018b). The confidence in the score is low as is unclear whether the etiology of the lethargy is neurological in nature or is due to a general state of discomfort following exposure to an irritating test material.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- ECHA 2020d
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: In an acute oral toxicity study, rats received single doses of L-lactic acid at 3,162, 3,548, 3,981, 4,467, 5,012, 5,623 and 6,310 mg/kg via gavage. Lethargy, ataxia, prostration, irregular breathing, piloerection and squinting were noted immediately after dosing to two days after dosing. The dose levels causing these effects were not specified (Klimisch Score 2, reliable with restrictions).
- U.S. EPA 2008
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: In an acute oral toxicity study, single gavage doses of L-lactic acid at 5,000 mg/kg caused ataxia, prostration, irregular breathing and squinting, which were observed up through day 2 post-exposure.
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: In an acute inhalation toxicity study, 4-hour exposure to L-lactic acid at 7.94 mg/L caused lethargy in some female animals during exposure, most of which subsidized by 24 hours. One female had rapid, shallow breathing and slight tremors on day 5 post-treatment.
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: In an acute dermal toxicity study, L-lactic acid at the single dose of 2,000 mg/kg induced local atonia at the application sites.
- Based on the weight of evidence, reversible lethargy possibly indicative of central nervous system depression was observed in animals exposed to relatively high doses of L-lactic acid. Therefore, ToxServices conservatively classified lactide as a Category 3 specific target organ toxicant following single exposures for narcotic effects under GHS criteria (UN 2019).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): *L*
Lactide was assigned a score of Low for neurotoxicity (repeated dose) based on the surrogate lactic acid being a normal metabolite in the body and it not being considered a repeat dose neurotoxicant. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is low as due to the limited availability of measured data and lack of authoritative listings.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).

- Clary et al. 2001
    - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4):* L-lactic acid is a natural component of metabolism and is not considered to be neurotoxic.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
Lactide was assigned a score of Low for skin sensitization based on the lack of skin sensitization identified in a local lymph node assay (LLNA). GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on measured data from a high quality study (GLP-compliant, internationally-accepted guideline).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a,b
    - A GLP-compliant mouse LLNA conducted according to OECD Guideline 429/EU Method B.42/EPA OPPTS 870.2600 was performed with female CBA/J mice (5/dose group) administered topical applications of L-lactide (99% purity) in dimethylformamide at 0, 10, 25, or 50% w/w to the dorsal surface of each ear for three consecutive days. Three days later, the mice were sacrificed and the draining auricular lymph nodes were isolated for the proliferation assay. The stimulation indices (SIs) were 2.1, 1.5 and 0.9 for the 10, 25 and 50% solutions, respectively. Since the test substance did not elicit an SI of 3, the authors concluded that L-lactide was not sensitizing to the skin under the tested condition (Klimisch Score 1, reliable without restriction).

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
Lactide was assigned a score of Low for respiratory sensitization based on the lack of dermal sensitization potential according to the ECHA guidance (2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when they are not GHS classified (CPA 2018b). Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2020
    - Lactide does not contain any structural alerts for respiratory sensitization (Appendix D).
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As lactide was not sensitizing to the skin (see skin sensitization section above), a literature search did not find any human evidence of respiratory sensitization by lactide, and as lactide does not contain any structural alerts for respiratory sensitization (OECD 2020), lactide is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): L
Lactide was assigned a score of Low for skin irritation/corrosivity based on the lack of dermal irritation detected in a rabbit study. GreenScreen® criteria classify chemicals as a Low hazard for skin

irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on measured data from a high quality study (GLP-compliant, internationally-accepted guideline).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a,b
  - A GLP-compliant dermal irritation test conducted according to OECD Guideline 404/EU Method B.4 was performed with New Zealand white rabbits (three total) administered topical applications of 0.5 g L-lactide (>99.5% purity) in water to shaved skin under semi-occlusive dressing for four hours. An observation period of 72 hours followed the exposure period. At 24, 48, and 72 hours, the mean erythema and edema scores were both zero. Therefore, the authors concluded that L-lactide was not irritating to the skin under the tested conditions (Klimisch Score 1, reliable without restriction).

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *H*

Lactide was assigned a score of High for eye irritation/corrosivity based on the majority of EU notifiers self-classifying it to GHS Category 2A with the Hazard Statement of H319. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they are classified as GHS Category 2A eye irritants (CPA 2018b). The confidence in the score is low as it is based on non-harmonized GHS classification.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020c
  - A majority of EU notifiers (53/72, 74%) self-classified L-lactide (CAS #4511-42-6) as a GHS Category 2 eye irritant (H319).
  - All of the EU notifiers (53/53, 100%) self-classified lactide (CAS #95-96-5) as a GHS Category 2 eye irritant (H319).
- ECHA 2020a,b
  - A GLP-compliant ocular irritation test conducted according to OECD Guideline 405/EU Method B.5 was performed with New Zealand white rabbits (three total) administered 0.01 mL powdered L-lactide (>99.5% purity) to the surface of the cornea (not instilled to the conjunctival sac). An observation period of seven days followed the exposure. At 24, 48, and 72 hours, the mean corneal opacity score was 0.43 (individual scores of 0, 1.3, and 0), the mean iris score was 0.1 (individual scores of 0, 0.3, and 0), the mean conjunctival redness score was 2 (individual scores of 0.3, 2.7, and 3.0), and the mean chemosis score was 1.13 (individual scores of 0, 1.7, and 1.7). All ocular irritation effects were fully reversible within seven days. The authors concluded that lactide was irritating to the eyes under the tested conditions and classified it as a GHS Category 2 ocular irritant (Klimisch Score 2, reliable with restrictions due to deviation from the guideline by using 0.01 mL instead of 0.1 mL as specified in the guideline in ECHA 2020b; Klimisch Score 1, reliable without restriction in ECHA 2020a).
    - Under GHS guidance (UN 2019), a chemical is classified as irritating to the eyes if it produces mean scores ≥ 1 for corneal opacity, ≥ 1 for iritis, ≥ 2 for conjunctival redness, and/or ≥ 2 for chemosis in at least 2 of 3 animals following readings at 24, 48, and 72 hours, with reversibility of the irritation effects occurring within 21 days (Category 2A) or 7 days (Category 2B). As L-lactide produced conjunctival redness

scores ≥ 2 in two of three animals that was fully reversible within seven days, ToxServices classified lactide as a GHS Category 2B ocular irritant.

- Based on the weight of evidence, a score of High was assigned. While the GLP-compliant eye irritation study indicates that lactide is a GHS Category 2B mild eye irritant, the study only tested 1/10th of the recommended test dose by OECD Guideline 405. It is likely that a higher dose would lead to a higher degree of eye irritation. The surrogate lactic acid is self-classified as a GHS Category 1 eye irritant in its REACH registration dossier (ECHA 2020d). However, lactic acid appears to be more irritating than lactide, as it is self-classified as a GHS Category 2 skin irritant based on reliable data on rabbits (ECHA 2020d), while data on L-lactide in rabbits demonstrate that L-lactide is not a dermal irritant, as previously described. Therefore, ToxServices did not consider lactic acid an appropriate surrogate for lactide for this endpoint, and relied on H319 assigned by the majority of the EU notifiers for lactide to score this endpoint.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L

Lactide was assigned a score of Low for acute aquatic toxicity based on modeled values ≥ 165.67 mg/L for lactide and measured values ≥ 130 mg/L for the surrogate lactic acid. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values are > 100 mg/L (CPA 2018b). The confidence in the score is high as it is based, in part, on measured data from high quality studies for the surrogate (GLP-compliant, nationally- or internationally-recognized guidelines).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S EPA 2017a
  - Lactide is designated to the esters ECOSAR chemical class (Appendix E). The most conservative predicted L/EC_{50} values are 165.67 mg/L (fish, 96-hr), 408.74 mg/L (daphnid, 48-hr), and 224.14 mg/L (algae, 96-hr).
- ECHA 2020a,b
  - All of the following studies were assigned Klimisch Score 2 (reliable with restrictions).
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: 96-hour LC_{50} (*Danio rerio*, zebra fish) = 195 mg/L (measured) (GLP-compliant, OECD Guideline 203)
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: 96-hour LC_{50} (*D. rerio*, zebra fish) > 320 mg/L (nominal) (GLP status not specified, OECD Guideline 203)
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: 96-hour LC_{50} (*Oncorhyncus mykiss*, rainbow trout) = 130 mg/L (nominal) (GLP status not specified, EPA-669/3-75-009)
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: 96-hour LC_{50} (*Lepomis macrochirus*, bluegill sunfish) = 130 mg/L (nominal) (GLP-compliant, EPA-669/3-75-009)
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: 48-hour mobility EC_{50} (*Daphnia manga*, daphnia) = 130 mg/L (measured) (GLP-compliant, OECD Guideline 202)
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: 48-hour mobility EC_{50} (*D. manga*, daphnia) = 750 mg/L (nominal) (GLP-compliant, EPA 660/3-75009)
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: 48-hour mobility EC_{50} (*D. manga*, daphnia) = 240 mg/L (nominal) (GLP-status not specified, OECD Guideline 202)

- *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: 72-hour EC_{50} (*Pseudokirchnerella subcapitata*, green algae) = 3,500 mg/L (growth rate), > 2,800 mg/L (biomass) (both nominal) (GLP-compliant, OECD Guideline 201)

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *L*

Lactide was assigned a score of Low for chronic aquatic toxicity based on estimated chronic aquatic toxicity values ≥ 17.44 mg/L for lactide and a measured chronic algal toxicity value of 1,900 mg/L for the surrogate lactic acid. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity value are > 10 mg/L (CPA 2018b). The confidence in the score is low as measured data are only available for the algae trophic level.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S EPA 2017a
  - Lactide is designated to the esters ECOSAR chemical class (Appendix E). The most conservative predicted ChV values are 17.44 mg/L (fish), 442.78 mg/L (daphnid), and 34.18 mg/L (algae).
- ECHA 2020a,b (studies with Klimisch scores of 3 (not reliable) were not included in this section)
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: 72-hour growth rate NOEC (*P. subcapitata*, green algae) = 1,900 mg/L (nominal) (GLP-compliant, OECD Guideline 201) (Klimisch Score 2, reliable with restrictions).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): L

Lactide was assigned a score of Low for persistence based on the surrogate lactic acid meeting the requirements for rapid biodegradability. GreenScreen® criteria classify chemicals as a Low hazard for persistence when they are rapidly biodegradable under GHS criteria (CPA 2018b). The confidence in the score is high as it is based, in part, on measured data from high quality studies (GLP compliant and/or internationally-accepted guideline).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2017b
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that lactide is expected to be readily biodegradable. Fugacity modeling (MCI Method) predicts 55.5% will partition to soil with a half-life of 720 hours (30 days), 38.3% will partition to water with a half-life of 360 hours (15 days), and 6.11% will partition to air with a half-life of 114 hours (4.75 days) (Appendix F).
- ECHA 2020d
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: In a GLP-compliant ready biodegradability test conducted according to EU Method C.5/C.6, non-adapted domestic activated sludge was exposed to lactic acid (80% aqueous solution) at 2 or 4 mg/L for 20 days. The test substance degraded 50% and 67% after 5 and 20 days, respectively. The BOD5 and BOD20 were 50% and 67% of COD, respectively, indicating that the chemical is readily biodegradable, but fails to meet the 10 day window (Klimisch Score 2, reliable with restrictions).
  - *Surrogate: Lactic Acid (CAS #50-21-5)/L-Lactic Acid (CAS #79-33-4)*: In a non-GLP-

compliant ready biodegradability test conducted according to EU Method C.5, non-adapted domestic activated sludge was exposed to lactic acid (purity not specified) at 5 mg/L for 20 days. The BOD 20 was 0.6 mg O_2 per mg test substance compared to a COD of 0.85 mg O_2 per mg test substance, indicating that it is readily biodegradable. However, it failed the 10-day window as the BOD5 *100/COD was only 50% (Klimisch Score 2, reliable with restrictions).

- Although experimental biodegradation studies indicate that lactic acid does not pass the 10-day window, it meets the criteria for "rapid degradability" under GHS. ToxServices considered these results in conjunction with modeled data, but placed more weight in the measured values. Modeling predicts that lactide is readily biodegradable, with a half-life of 30 days in soil, its dominant environmental compartment. Collectively, these data suggest that lactic acid, and thus lactide, meets the criteria for rapid degradability, and therefore a score of Low was assigned.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Lactide was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of 0.4 and an estimated BCF of 0.9408. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when log K_{ow} values are no greater than 4 and BCF values are no greater than 100 (CPA 2018b). The confidence in the score is high as it is based, in part, on a measured log K_{ow} value.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a,b
  - DL-Lactide (CAS #95-96-5) has a log K_{ow} of 0.4 at 25°C and neutral pH as measured in a GLP-compliant OECD Guideline 117/EU Method A.8/EPA OPPTS 830.7570 test (Klimisch Score 2, reliable with restrictions).
- U.S. EPA 2017b
  - BCFBAF predicts a BCF of 3.162 L/kg wet-wt using the regression-based method, and an estimated BCF of 0.9408 using the Arnot-Gobas method for the upper trophic level and considering biotransformation, for lactide, based on a measured log K_{ow} of 0.4 (Appendix F).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Lactide was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score was low as it is not based on measured data or authoritative lists.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Futerro 2009
  - Lactide is stable under normal operating conditions of storage, handling, and use. This chemical will react with water to form lactic acid.
- Fisher Scientific 2018
  - A safety data sheet for a product containing > 95% L-lactide indicates it has an NFPA instability rating of 0 ("Normally stable, even under fire exposure conditions, and is not reactive with water (e.g. helium, N_2").

- Based on the above information, ToxServices did not classify lactide as a reactive substance under GHS criteria (UN 2019).

Flammability (F) Score (vH, H, M, or L): L

Lactide was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable solid under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is available (CPA 2018b). The confidence in the score was high as it is based, in part, on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020b
  - L-Lactide (CAS #4511-42-6) was non-flammable in a GLP-compliant EU Method A.10 (Flammability (Solids)) test. No propagation or combustion of the test substance along 200 mm length of pile within 4 minutes was observed, and it did not ignite in contact with air (Klimisch Score 1, reliable without restriction).
- Fisher Scientific 2018
  - A safety data sheet for a product containing > 95% L-lactide indicates it has an NFPA flammability rating of 1 ("Materials that require considerable preheating, under all ambient temperature conditions, before ignition and combustion can occur (e.g. mineral oil, ammonia). Includes some finely divided suspended solids that do not require heating before ignition can occur. Flash point at or above 93.3°C (200°F)").
- Since the above data indicate that lactide is not flammable or required pre-heating for ignition to occur, ToxServices did not classify lactide as a flammable solid under GHS criteria (UN 2019).

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No	Lactide	4511-42-6; 615-95-2	L	L	*L*	*L*	*L*	L	L	L	*M*	*L*	L	*L*	L	*H*	L	*L*	L	vL	*L*	L

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	No	No	No
3	No	No	Yes	No			
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Lactide	3

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Lactide	3

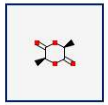
After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2												
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		3
4												

APPENDIX C: Pharos Output for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)

CAS #4511-42-6:



4511-42-6

Lactide, L-

ALSO CALLED [13167-47-0] Lactide, L- (primary CASRN is 4511-42-6), [17699-81-9] Lactide, L- (primary CASRN is 45...

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Pharos Hazards View

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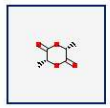
ENDPOINT	HAZARD LEVEL	HAZARD LIST	HAZARD DESCRIPTION	OTHER LISTS
Restricted list	Potential Concern	EU - PACT-RMOA Substances	Substances selected for RMOA or hazard assessment	
Eye irritation	Potential Concern	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified)	
Skin irritation	Potential Concern	EU - Manufacturer REACH hazard submissions	H314 - Causes severe skin burns and eye damage (unverified)	
Multiple	Potential Concern	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	

APPENDIX C: Pharos Output for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0), ctd.

CAS #615-95-2:



615-95-2

Dilactide (primary CASRN is 95-96-5)

ALSO CALLED [95-96-5] Dilactide, (-)-L-Dilactide, (+/-)-3,6-Dimethyl-1,4-dioxane-2,5-dione, (3R-Cis)-3,6-Dimethy...

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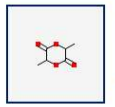
ENDPOINT	HAZARD LEVEL	HAZARD LIST	HAZARD DESCRIPTION	OTHER LISTS
Restricted list	Potential Concern	EU - PACT-RMOA Substances	Substances selected for RMOA or hazard assessment *	
Eye irritation	Potential Concern	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) *	
Multiple	Potential Concern	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters *	

APPENDIX C: Pharos Output for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0), ctd.

CAS #95-96-5:



95-96-5
Dilactide
ALSO CALLED [116559-43-4] Dilactide (primary CASRN is 95-96-5), [137566-94-0] Dilactide (primary CASRN is 95-96-...
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Pharos Hazards View

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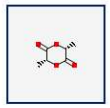
ENDPOINT	HAZARD LEVEL	HAZARD LIST	HAZARD DESCRIPTION	OTHER LISTS
Restricted list	Potential Concern	EU - PACT-RMOA Substances	Substances selected for RMOA or hazard assessment	
Eye irritation	Potential Concern	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified)	
Multiple	Potential Concern	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	

APPENDIX C: Pharos Output for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0), ctd.

CAS #13076-17-0:



13076-17-0

Lactide, D-

ALSO CALLED [17699-82-0] Lactide, D- (primary CASRN is 13076-17-0), (3R-Cis)-3,6-Dimethyl-1,4-dioxane-2,5-dione,...

View all synonyms (12)

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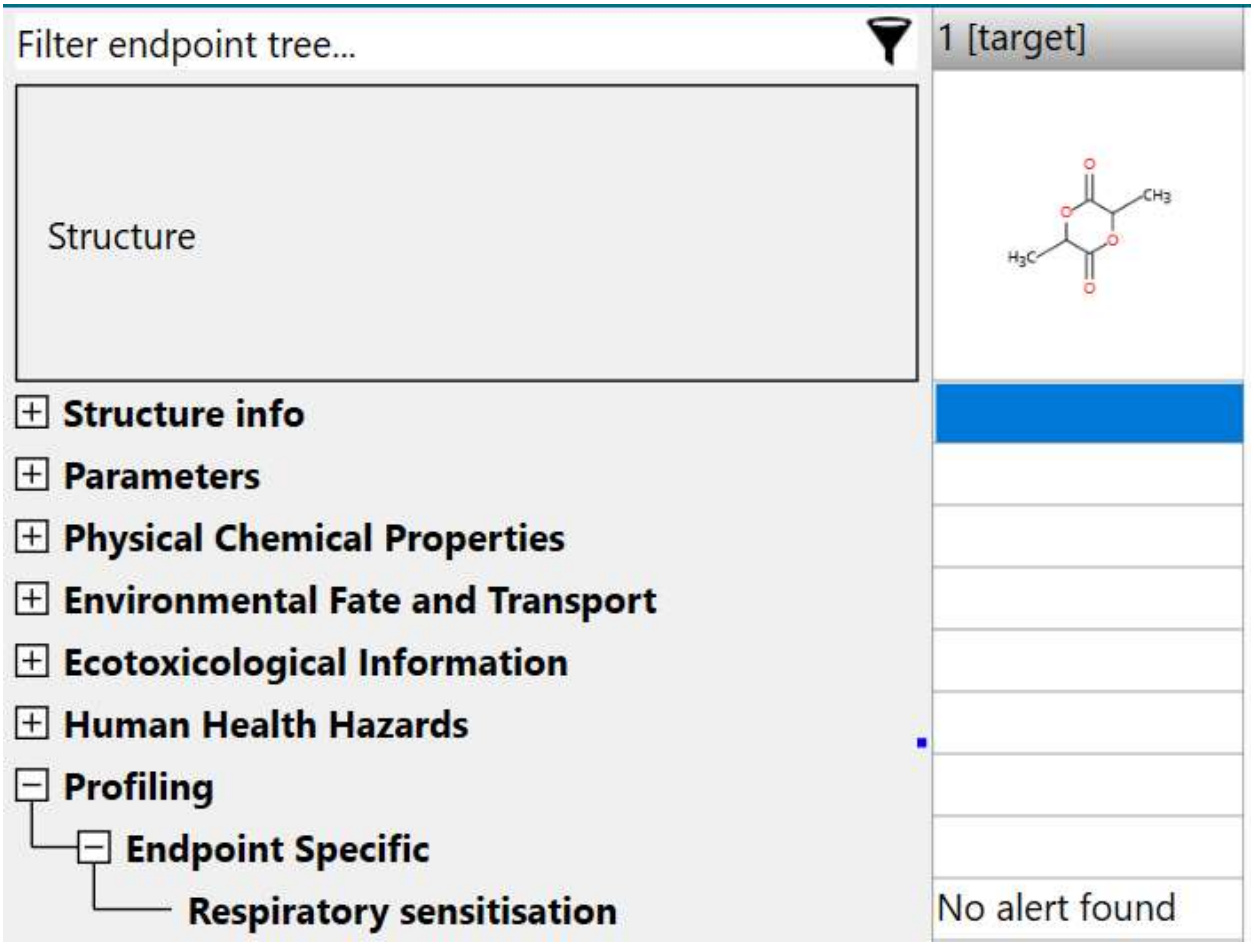
Pharos Hazards View

Download Lists

ENDPOINT	HAZARD LEVEL	HAZARD LIST	HAZARD DESCRIPTION	OTHER LISTS
Restricted list	Potential Concern	EU - PACT-RMOA Substances	Substances selected for RMOA or hazard assessment	
Multiple	Potential Concern	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	

APPENDIX D: OECD Toolbox Respiratory Sensitization Results for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)



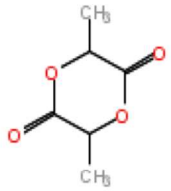
APPENDIX E: ECOSAR Modeling Results for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
95965	1,4-Dioxane-2,5-dione, 3,6-dimethyl-	O=C(OC(C(=O)O1)C)C1C

Structure



Details	
Mol Wt	144.13
Selected LogKow	0.4
Selected Water Solubility (mg/L)	22531.31
Selected Melting Point (°C)	97
Estimated LogKow	1.65
Estimated Water Solubility (mg/L)	22531.31
Measured LogKow	
Measured Water Solubility (mg/L)	
Measured Melting Point (°C)	117.5

Class Results:	

Esters

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	165.67	5	
Daphnid	48h	LC50	408.74	5	
Green Algae	96h	EC50	224.14	6.4	
Fish		ChV	17.44	8	
Daphnid		ChV	442.78	8	
Green Algae		ChV	34.18	8	
Fish (SW)	96h	LC50	277.98	5	

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Mysid	96h	LC50	601.46	5	
Fish (SW)		ChV	29.87	8	
Mysid (SW)		ChV	1153901.5	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Earthworm	14d	LC50	6162.95	6	

APPENDIX F: EPI Suite™ Modeling Results for Lactide (CAS #4511-42-6; 615-95-2; 95-96-5; 13076-17-0)

(Estimated values included in the GreenScreen® are highlighted and bolded)

CAS Number: 95-96-5
SMILES : O=C(OC(C(=O)O1)C)C1C
CHEM : 1,4-Dioxane-2,5-dione, 3,6-dimethyl-
MOL FOR: C6 H8 O4
MOL WT : 144.13
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 0.40
Boiling Point (deg C) : 266.00
Melting Point (deg C) : 97.00
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): 16
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 1.65

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 307.80 (Adapted Stein & Brown method)
Melting Pt (deg C): 26.08 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.00233 (Modified Grain method)
VP (Pa, 25 deg C) : 0.311 (Modified Grain method)
MP (exp database): 117.5 deg C
BP (exp database): 142 @ 8 mm Hg deg C
Subcooled liquid VP: 0.0116 mm Hg (25 deg C, Mod-Grain method)
: 1.55 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 2.253e+004
log Kow used: 0.40 (user entered)
melt pt used: 97.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 72424 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found: Esters

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.22E-005 atm-m3/mole (1.24E+000 Pa-m3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:

HLC: 2.762E-005 atm-m3/mole (2.798E+000 Pa-m3/mole)
VP: 0.00233 mm Hg (source: MPBPVP)
WS: 16 mg/L (source: User-Entered)
Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 0.40 (user entered)
Log Kaw used: -3.302 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 3.702
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.0273
Biowin2 (Non-Linear Model) : 0.9999
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.1611 (weeks)
Biowin4 (Primary Survey Model) : 4.0977 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.8866
Biowin6 (MITI Non-Linear Model): 0.9461
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 1.0995
Ready Biodegradability Prediction: YES

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 1.55 Pa (0.0116 mm Hg)
Log Koa (Koawin est): 3.702
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 1.94E-006
Octanol/air (Koa) model: 1.24E-009
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 7.01E-005
Mackay model : 0.000155
Octanol/air (Koa) model: 9.89E-008

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 2.2590 E-12 cm3/molecule-sec
Half-Life = 4.735 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 56.817 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.000113 (Junge-Pankow, Mackay avg)
9.89E-008 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):

Koc : 10 L/kg (MCI method)
Log Koc: 1.000 (MCI method)
Koc : 10.36 L/kg (Kow method)
Log Koc: 1.015 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -2.7894 days (HL = 0.001624 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.026 (BCF = 0.9408)
Log BAF Arnot-Gobas method (upper trophic) = -0.026 (BAF = 0.9408)
log Kow used: 0.40 (user entered)

Volatilization from Water:
Henry LC: 1.22E-005 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 58.84 hours (2.452 days)
Half-Life from Model Lake : 742.6 hours (30.94 days)

Removal In Wastewater Treatment:
Total removal: 2.52 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.75 percent
Total to Air: 0.68 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**6.11**	**114**	**1000**
Water	**38.3**	**360**	**1000**
Soil	**55.5**	**720**	**1000**
Sediment	0.0863	3.24e+003	0

Persistence Time: 379 hr

Level III Fugacity Model: (MCI Method with Water percents)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.11	114	1000
Water	38.3	360	1000
water	(38.3)		
biota	(4.81e-006)		
suspended sediment	(0.000575)		
Soil	55.5	720	1000
Sediment	0.0863	3.24e+003	0

Persistence Time: 379 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.92	114	1000
Water	44.9	360	1000
water	(44.9)		
biota	(5.64e-006)		
suspended sediment	(6.94e-005)		
Soil	48.1	720	1000
Sediment	0.0842	3.24e+003	0
Persistence Time: 346 hr			

Licensed GreenScreen® Profilers

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