Method Version: GreenScreen® Version 1.2

Verified or Non-Verified: VERIFIED

Date of Verification:	**October 22, 2013**
Expiration Date:	**October 22, 2016**
Uses:	This complete report may be freely published and distributed by BizNGO.
Restrictions:	Clean Production Action does not confer licensing rights or authorize the use of the GreenScreen trademark on public or promotional materials for individual products comprised of the chemical assessed in this report. Any promotional use of the GreenScreen trademarks must be covered under a separate license agreement.
GreenScreen® Verification Performed By:	Clean Production Action
	Date: October 22, 2013
	Verification Review Plan Prepared By: Dr. Eric Rosenblum
Verified GreenScreen® Prepared by Licensed Profiler:	Organization: ToxServices LLC
	Date: October 15, 2013

Lactide (CAS #4511-42-6; 615-95-2) GreenScreen™ Assessment

Prepared for:

Clean Production Action

Date:

October 15, 2013 (Verified)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1367 Connecticut Ave., N.W., Suite 300
Washington, D.C. 20036

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

GreenScreen™ Executive Summary for Lactide (CAS #4511-42-6 and 615-95-2)

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.

Lactide was assigned a GreenScreen™ Benchmark Score of 2 ("Use but Search for Safer Substitutes") as it was assigned a score of High for Skin Irritation (IrS) and a score of Very High for Eye Irritation (IrE) for Group II Human (Appendix B). This corresponds to GreenScreen™ benchmark classification 2f in CPA 2011. A data gap (DG) exist on Respiratory Sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), lactide meets requirements for a GreenScreen™ Benchmark Score of 2 despite the hazard data gap. In a worst-case scenario, if lactide were assigned a High score for the data gap SnR*, it would still be categorized as a Benchmark 2 Chemical.

GreenScreen™ Benchmark Score for Relevant Route of Exposure:
All exposure routes (oral, dermal and inhalation) were evaluated together, as a standard approach for GreenScreen™ evaluations, so the GreenScreen™ Benchmark Score of 2 ("Use but search for safer substitutes") is applicable for all routes of exposure.

GreenScreen™ Hazard Ratings 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	repeated*	single	repeated*										
L	**L**	*L*	**L**	*L*	**L**	**L**	**L**	**M**	*L*	**L**	DG	**H**	**vH**	*M*	*M*	*M*	*vL*	**L**	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. 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. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen™ Assessment for Lactide (CAS #4511-42-6; 615-95-2)[1]

GreenScreen™ Version 1.2 Draft Assessment
Note: Validation Has Not Been Performed on this GreenScreen™ Assessment

Chemical Name: Lactide

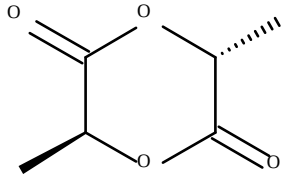
CAS Number: 4511-42-6; 615-95-2

GreenScreen™ Assessment Prepared By:
Name: Kristen Schaefer, M.F.S. and Zachariah Guerrette, Ph.D.
Title: Associate Toxicologist (K.S.) and Toxicologist (Z.G.)
Organization: ToxServices LLC
Date: March 1, 2013; October 14, 2013 (Revision #1)

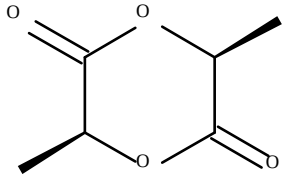
Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: March 11, 2013; October 15, 2013 (Revision #1)

Confirm application of the *de minimus* rule[2]: not applicable; lactide is not a mixture.
Chemical Structure(s):

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



D-Lactide (CAS #615-95-2)



Also Called: AI3-05059; 3,6-Dimethyl-1,4-dioxane-2,5-dione; 3,6-Dimethyl-2,5-dioxo-1,4-dioxane; EINECS 202-468-3; Lactic acid, bimol. cyclic ester; Lactide; NSC 403080; Propanoic acid, 2-hydroxy-, bimol. cyclic ester; UNII-7EH08MWO6M (ExPub 2013)

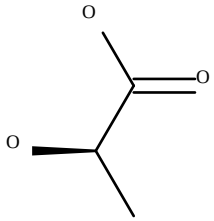
Notes related to production-specific attributes[3]: No information disclosed.

[1] Lactide has two stereoisomeric forms. The CAS #4511-42-6 refers to L-lactide while CAS #615-95-2 refers to D-lactide. CAS #95-96-5 is an additional registry number for the D-lactide stereoisomer (ChemIDplus 2013a).
[2] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

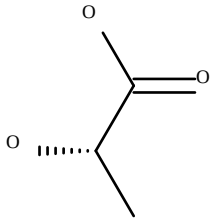
[3] Note any composition or hazard attributes of the chemical product relevant to how it is manufactured. For example, certain synthetic pathways or processes result in typical contaminants, by-products or transformation products. Explain any differences between the manufactured chemical product and the GreenScreen™ assessment of the generic chemical by CAS #.

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen™:

Lactic acid (CAS #50-21-5)



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



Data gaps exist for the majority of health effect endpoints. In order to address these data gaps, toxicity data for chemical surrogates were evaluated. 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. These two chemicals are expected to have similar chemistry, so lactic acid was used as a surrogate to address the data gaps for lactide.

Identify Applications/Functional Uses (Futerro 2013):
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 (transesterificaiton, amidation, ring opening polymerization, etc.)
5. Destabilitizer for production of porous ceramics
6. Electrolyte in lithium batteries

GreenScreen™ Summary Rating for Lactide[4]: Lactide was assigned a GreenScreen™ Benchmark Score of 2 ("Use but Search for Safer Substitutes") as it was assigned a score of High for Skin Irritation (IrS) and a score of Very High for Eye Irritation (IrE) for Group II Human (Appendix B). This corresponds to GreenScreen™ benchmark classification 2f in CPA 2011. A data gap (DG) exist for Respiratory Sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), lactide meets requirements for a GreenScreen™ Benchmark Score of 2 despite the hazard data gap. In a worst-case scenario, if lactide were assigned a High score for the data gap SnR*, it would still be categorized as a Benchmark 2 Chemical.

Figure 1: GreenScreen™ Hazard Ratings 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	repeated*	single	repeated*										
L	L	*L*	L	*L*	L	L	L	M	*L*	L	DG	H	vH	*M*	*M*	*M*	*vL*	L	L

[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.

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. 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. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings:

Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern[5,6]

Combustion of lactide can produce CO and CO_2. As they are naturally occurring in the environment, they are not considered relevant to the GreenScreen™ evaluation of the parent compound. ToxServices conducted a full GreenScreen™ on lactic acid (CAS #50-21-5), since lactide may form lactic acid when in the presence of water (Futerro 2013), and determined that it has a benchmark score of 2. Since the benchmark scores of the parent compound and the transformation product are the same, no changes are made to the benchmark score of the parent compound.

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	List Translator Results[7,8]
Food Additive	End	Hydrolysis with water	Lactic acid	50-21-5	LT-U

Introduction

Lactide is the monomer used to synthesis polylactic acid, a biocompatible and biodegradable plastic (Futerro 2012). Lactide is produced by the oligomerisation of lactic acid followed by cyclisation. Lactide has two stereoisomer forms: L-lactide (CAS #45411-42-6) and D-lactide (CAS #615-95-2). Limited toxicity data were available for lactide. Lactic acid (CAS #50-21-5) and its enantiomer, L-lactic acid (CAS #79-33-4), were selected as surrogates to fill any data gaps. These chemicals were selected due to the fact that lactide may form lactic acid when in the presence of water (Futerro 2013). In addition, lactic acid is a more conservative surrogate as it is a smaller molecule and therefore more reactive.

ToxServices assessed lactide against GreenScreen™ Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.37 (GreenScreen Hazard Assessment) (ToxServices 2013). In order to identify relevant environmental fate, environmental toxicity, and human health effects data, multiple sources were searched for data. These sources include on-line databases such as: ChemIDplus (which indexes databases such as HSDB, DART, EMIC, CCRIS, IRIS, Medline, and

[5] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.
[6] The assessment of transformation products depends on the Benchmark Score of the parent chemical (see CPA Guidance 2013).
[7] The GreenScreen™ List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen™ benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2013) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[8] The assessment of transformation products depends on the Benchmark Score of the parent chemical (see CPA Guidance 2013).

Toxline), TSCATS (which catalogs toxicity studies submitted to EPA under TSCA), ExPub (which indexes databases such as RTECS, NICNAS and ECHA. In addition, the World Wide Web is also used to search for material safety data sheets (MSDS) and other relevant data.

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 2012b). Pharos (Pharos 2013) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. The Pharos output indicates benchmark or possible benchmark scores for each human health and environmental endpoint.

- Lactide (CAS #4511-42-6; 615-95-2) is not present in the Pharos database.

PhysioChemical Properties of Lactide

Lactide is an organic chemical with chemical formula $C_6H_8O_4$ and molecular weight 114.13 g/mol. It is nearly odorless, white crystalline solid at room temperature. It is soluble in water at 20 °C and has an estimated log K_{OW} of 1.65. It is not expected to bioaccumulate in biota due to its low lipiphilicity.

Table 1: Physical and Chemical Properties of Lactide (CAS #4511-42-6; 615-95-2)

Property	Value	Reference
Molecular formula	$C_6H_8O_4$	ChemIDplus 2013b
SMILES Notation	C1(O[C@@H](C)C(O[C@@H]1C)=O)=O (L-lactide) C1([C@@H](OC(=O)[C@@H](O1)C)C)=O (D-lactide)	ChemIDplus 2013b ChemIDplus 2013a
Molecular weight	144.13 g/mol	Futerro 2010
Physical state	Solid	Futerro 2010
Appearance	White crystals	Futerro 2010
Melting point	98.7˚C	Futerro 2010
Vapor pressure	Not identified	
Water solubility	Soluble at 20 °C	Futerro 2010
Dissociation constant	Not identified	
Density/specific gravity	Not identified	
Partition coefficient	Log K_{OW} = 1.65 (estimated)	U.S. EPA 2012a

Hazard Classification Summary Section:

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 negative findings in studies using the chemical surrogates, L-lactic acid (CAS #79-33-4) or calcium lactate (CAS #814-80-2). Level of confidence was high due to the use of measured data on high confidence surrogates. GreenScreen™ criteria classify chemicals as a Low hazard for carcinogenicity when adequate surrogate data are available and negative, chemicals have no structural alerts and they are not classified by GHS (CPA

2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- No data was identified for Lactide
- Data available for the surrogate Lactic Acid:
  - ECHA 2013 –
    - In a 5-13-month study in rabbits, animals received L-lactic acid (CAS #79-33-4) 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.
    - In a 2-year carcinogenicity study (GLP status unknown), F344 rats (50/dose/sex) received calcium lactate, a food additive (CAS #814-80-2), 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). Body weight, water consumption, clinical signs, mortality, hematology, clinical chemistry, organ weights, gross pathology and histopathology were evaluated. No statistically significant dose-related increase of tumor incidences was found in any organ or tissue. The results indicated that calcium lactate was neither toxic nor carcinogenic to rats in the study.

Although no data were identified for lactide, the surrogates lactic acid and calcium lactate tested negative for carcinogenicity in rabbits and rats. Therefore, lactide is unlikely to be carcinogenic.

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

Lactide was assigned a score of Low for mutagenicity/genotoxicity based on negative findings for mutagenicity and chromosomal aberration in *in vitro* studies using the chemical surrogate, lactic acid. Level of confidence was high due to the use of data on high confidence surrogates. GreenScreen™ criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate surrogate data are available and are negative for both chromosomal aberrations and gene mutations (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- No data was identified for lactide
- Data available for the surrogate Lactic Acid:
- U.S. EPA 2008 –
  - In a study conducted by the National Toxicology Program (NTP), lactic acid (CAS #50-21-5) was not mutagenic in *Salmonella typhimurium* tester strains TA 97, TA 98, TA100 and TA1535 at concentrations up to 10,000 µg/plate in the presence and absence of metabolic activation.
  - In an *in vitro* chromosome aberration assay, lactic acid (CAS #50-21-5) was not clastogenic in Chinese hamster ovary cells at the concentrations up to 35 mM with and without metabolic activation.

Although no data were identified for lactide, data on the surrogate lactic acid indicate that it was not mutagenic in bacteria or clastogenic in mammalian cells. Therefore, lactide is unlikely to be mutagenic.

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

Lactide was assigned a score of *L* for reproductive toxicity based on limited negative data in rats and expert judgment on the surrogate lactic acid. GreenScreen™ criteria classify chemicals as a *Low* hazard for reproductive toxicity when there is limited evidence of no adverse reproductive effects (CPA 2012a). This hazard score is considered to be low confidence based on the lack of detail available for the study identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- No data were identified for lactide and limited data are available for lactic acid. However, testing for lactic acid is not deemed necessary because the substance is a normal component of human intermediary metabolism (U.S. EPA 2008).
- D'Amour 1934
  - 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.
    - 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.
- Lactic acid is a normal component of mammalian metabolism. 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 negative findings in mice exposed orally to the chemical surrogate, lactic acid (50-21-5), at dose levels up to 570 mg/kg/day. Level of confidence was high due to the use of high confidence surrogates. GreenScreen™ criteria classify chemicals as a Low hazard for developmental toxicity when adequate surrogate data are available and negative, no structure alerts are present and they have not been classified by GHS (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- U.S. EPA 2008 –
  - Lactic acid was administered to pregnant CD-1 mice via gavage at doses of 0 or 570 mg/kg/day during days 6-15 of gestation. No maternal or developmental effects were seen at this dose. No further details were provided. The maternal and development NOAELs were established as 570 mg/kg/day based on the lack of effects observed at up to the highest dose tested.

Although no data were identified for lactide, its surrogate lactic acid did not induce developmental toxicity at the dose of 570 mg/kg/day. Therefore, lactide is unlikely to be a developmental toxicant.

Endocrine Activity (E) Score (H, M or L): *L*
Lactide was assigned a score of *L* for endocrine disruption based on an assessment by the U.S. EPA that lactic acid and its metabolites are not expected to cause adverse effects to the endocrine system. GreenScreen™ criteria classify chemicals as a Low hazard for endocrine activity when adequate data are available and negative, no structure alerts are present and they have not been classified by GHS (CPA 2012a). This hazard score is considered to be low confidence based on the lack of experimental data available on lactide or its surrogates for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- No data were identified for lactide or lactic acid.
- U.S. EPA 2009
  - 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 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

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} values greater than 2,000 mg/kg. GreenScreen™ criteria classify chemicals as a Low hazard for acute toxicity when they have been assigned oral and/or acute LD_{50} values greater than 2,000 mg/kg (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- ChemIDplus 2013a –
  - Oral LD_{50} (rat) > 5,000 mg/kg
  - Dermal LD_{50} (rabbit) > 2,000 mg/kg

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
***Group II Score (single dose)* (vH, H, M or L)**: **L**
Lactide was assigned a score of Low for systemic toxicity (single dose) based on the lack of systemic toxic effects at oral doses up to 2,000 mg/kg, dermal doses up to 2,000 mg/kg and inhalation doses up to 7.94 mg/L (4-hour exposure). Level of confidence was high due to the use of high confidence surrogates. GreenScreen™ criteria classify chemicals as a Low hazard for systemic toxicity (single

dose) when systemic adverse effects are not observed at oral doses less than 2,000 mg/kg, at dermal doses less than 2,000 mg/kg, and inhalation doses less than 10 mg/L (4-hour exposure) (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- ECHA 2013 –
  - In an acute oral toxicity study performed under GLP according to Guideline EPA OPP 81-1, L-lactic acid was administered to albino rats (5/dose/sex) via gavage (vehicle: water) at single doses of 3,162, 3,548, 3,981, 4,467, 5,012, 5,623 or 6,310 mg/kg. The testing duration was 14 days for range-finding (doses unspecified but at least included 1,000, 1,585, 2,512 and 3,981 mg/kg) and 14 days or less for each main study dose level. Mortality, clinical signs, body weight and gross pathology were evaluated. Deaths in females were 1/5, 2/5, 5/5, 5/5, 5/5, 5/5 and 5/5 for each dose group. Deaths in males were 0/5, 0/5, 0/5, 1/5, 3/5, 4/5 and 5/5. Lethargy, ataxia, prostration, irregular breathing, piloerection, squinting, lacrimation, salivation, crusty eyes and muzzle, loose stools, damp or yellow/brown stained fur, and moribund were observed as early as 0–1 hour after dosing and as late as day 2. Body weights were increased consistently on days 7 and 14 for all surviving animals. Abnormal pathology observed at necropsy in animals found dead and in the 4 surviving females at 3,162 mg.kg group were discolored lungs, firm texture of lungs, green foci on the lung, several stomach lesions, discolored liver, white foci on the liver, pale capsular areas, superficial erosion or mottled liver, discolored kidney and red-brown exudate in the nasal and/or oral regions. No other abnormalities were observed during necropsy of all main study animals.
- U.S. EPA 2008 –
  - In an acute oral toxicity study, Charles River rats (5/sex) received L-lactic acid via gavage at 5,000 mg/kg in water and were observed for up to 14 days. One male and all females died on the day of dosing, day 1 or day 10. Four males survived the 14-day study. Three of the surviving animals had body weight gains while one had a small weight loss. All the animals that were found dead had reduced body weights. Clinical signs for some animals on the day of dosing up through day 2 were ataxia, prostration, irregular breathing, squinting, lacrimation, crusty eyes, crusty nose and a body cool to touch.
  - In an acute inhalation toxicity study, Fischer 344 rats (5/sex/dose) were exposed nose-only to L-lactic acid as an aerosol at 7.94 mg/L for 4 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. No gross lesions were observed at necropsy.
  - In an acute dermal toxicity study, male and female New Zealand White rabbits (10 total) were dermally administered L(+) lactic acid in water to clipped, abraded skin at 2,000 mg/kg under occlusive conditions for 2 hours and observed for 14 days. All animals survived and gained weight during the study period. No abnormal clinical signs were found. Severe erythema and edema were found in all animals on day 1 at the application

sites. The severity of erythema decreased in 3 animals by day 12 or 14 and not present for 1 female on day 14. The severity of edema decreased in 8 animals and absent in 1 female on day 12 and in 1 male on day 14. Other local effects included blanching, necrosis, eschar formation, atonia, desquamation and denuded areas. A dark red focus was observed on the lung of one male.

- HSDB 2006 –
  - Several cases of acetic acid, trichloracetic acid and lactic acid poisoning all reported esophageal strictures and gastric lesions.
  - In general, on the basis of animal studies and human use, the most significant effects of lactate esters are respiratory, dermal and ocular irritation which may be associated with the formation of lactic acid, a product of hydrolysis of lactate esters.
- Based on the weight of evidence, lactic acid is practically non-toxic to animals via the oral route of exposure with irreversible adverse effects observed at doses higher than 2,000 mg/kg. For the inhalation route of exposure, most of the animals survived the 4-h dose of 7.94 mg/L and recovered from symptoms by day 14. Although, 1 animal died during the inhalation study and this mortality appeared to be related to the treatment, no gross lesions were observed during necropsy and the cause of death was not identified. For the dermal route of exposure, only local signs of irritation without significant systemic toxicity were observed at 2,000 mg/kg. Reversible narcotic effects were observed in some animals after oral and inhalation exposure and are discussed in the Neurotoxicity section below. Respiratory irritation may occur in humans.

Group II* Score (repeated dose) **(H, M, or L): L**

Lactide was assigned a score of Low for Systemic Toxicity (Repeated Dose) based on lack of systemic toxicity observed at doses of 100 mg/kg/day or less. GreenScreen™ criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when assigned a LOAEL that is greater than 100 mg/kg/day (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- Herbert et al. 1999 –
  - A 2-week study was performed with beagle dogs administered oral doses of lactide of 0, 10, 100, 400, 1,000 and 2,500 mg/kg/day via gelatin capsules. No mortality was observed over the course of the study. Clinical signs consistent with irritation of the alimentary tract were observed in dogs in the 1,000 and 2,500 mg/kg/day dose groups. Reduced body weight gain and absolute and relative thymus weights were also observed in the 1,000 and 2,500 mg/kg/day groups. Reduced absolute and relative spleen weights were also observed in the 2,500 mg/kg/day dose group. These effects were considered 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. ToxServices identified the LOAEL for this study as 1,000 mg/kg/day based on irritation in the gastrointestinal tract observed in dogs administered 1,000 or 2,500 mg/kg/day.
  - A 13-week oral feed study was conducted in beagle dogs administered oral doses of lactide of 0, 4, 20 or 100 mg/kg/day. No clinical signs of toxicity or mortality were observed, and there were no treatment-related effects on body weights, food consumption, or any of the clinical chemistry, hematology or urinalysis parameters.

Gross and microscopic findings considered to be treatment-related were minimal, and were limited to a stomach focus in one dog of each sex in the 100 mg/kg group. Microscopic evaluation of the stomach focus in the 100 mg/kg female dog identified it as a stomach ulcer. These results demonstrated that the primary toxic effect of lactide was irritation of the gastrointestinal tract, and the authors identified the NOAEL as 100 mg/kg/day based on these effects. It should be noted, however, that no information was available regarding the sample size and no statistical analysis was available in the abstract for this study.

In two repeated dose oral toxicity studies on lactide, no systemic toxicities were found in rats (up to 1,000 mg/kg/day) and dogs (up to 100 mg/kg/day). The only effects observed were related to local irritation.

Neurotoxicity (N)

Group II Score (single dose)**(vH, H, M or L): M**

Lactide was assigned a score of Moderate for neurotoxicity (single dose) based on lethargic effects in single-dose studies in animals using the surrogate, L-lactic acid (CAS #79-33-4), which classify the chemical as GHS Category 3 Single Exposure. Level of confidence was high due to the use of high confidence surrogates. GreenScreen™ criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when they are classified as GHS Category 3 Single Exposure (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- ECHA 2013 –
  - In an acute oral toxicity study, rats received single doses of L-lactic acid at 3162, 3548, 3981, 4467, 5012, 5623 and 6310 mg/kg via gavage. Lethargy, ataxia, prostration, irregular breathing, piloerection and squinting were noted.
- U.S. EPA 2008 –
  - 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 were observed up through day 2 post exposure.
  - 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.
  - 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 indicative of central nervous depression was observed in animals exposed to relatively high doses of L-lactic acid.

Group II* Score (repeated dose) **(H, M, L):** *L*

Lactide was assigned a score of *L* for neurotoxicity (repeat dose) based on it 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 (repeat dose) when there are adequate data and negative studies, no structural alerts, and no classification under GHS are available (CPA 2012a). This hazard score is considered to be low confidence based on the lack of experimental data available for this endpoint for lactide or its surrogates.

- Authoritative and Screening Lists

  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- No data were identified.
- Clary et al. 2001
  - 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 Low for Skin Sensitization (SnS) based on the negative results for dermal sensitization obtained from administration of the surrogate lactic acid to guinea pigs. Level of confidence was high due to the use of high confidence surrogates. GreenScreen™ criteria classify chemicals as a L hazard for skin sensitization when adequate data are available and negative, no structure alerts are present and they have not been classified by GHS (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- No data were identified for lactide.
- Data for lactic acid:
  - ECHA 2013 –
    - Lactic acid was not sensitizing in female Hartley guinea pigs in a Buehler test performed according to the Guideline EPA OPP 81-6 under GLP.
    - Lactic acid was not sensitizing to guinea pigs in a Guinea pig maximization test. No further information was provided

Although no data were found on lactide, its surrogate lactic acid tested negative for skin sensitization in guinea pigs. Therefore, lactide is unlikely to be a skin sensitizer.

Respiratory Sensitization (SnR) Group II* Score (H, M or L): DG
Lactide was assigned a Data Gap for Respiratory Sensitization (SnR) based on the lack of data available for either lactide or the surrogate lactic acid for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- No data were identified for lactide or the surrogate lactic acid.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M or L): H
Lactide was assigned a score of H for skin irritation/corrosivity based on the classification as a GHS Category 2 skin irritant. GreenScreen™ criteria classify chemicals as a High ("H") hazard for skin irritation/corrosivity when classified as GHS Category 2 skin irritants and associated with the EU R-Phrase 37/38 (CPA 2012a). Data for the surrogate lactic acid supports the assignment of this score based on the observation of up to severe irritation in two of seven studies.

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists

- Futerro 2010 –
    - Lactide is classified as a GHS Category 2 skin irritant, H315 – causes skin irritation.
    - Lactide is associated with the EU Risk Phrase R37/38: Irritating to respiratory system and skin
- Data on surrogate lactic acid:
    - U.S. EPA 2008 –
        - Buffered lactic acid was not irritating to rabbit skin (occlusive, 4 hours, intact skin)
        - *L(+) lactic acid:* The chemical (0.5 mL of an 88% solution) was severely irritating and corrosive to rabbit skin (occlusive, 4-h, intact and abraded skin).
        - *L(+) lactic acid:* The chemical (0.5 mL of an 80% solution) was severely irritating and corrosive to rabbit skin (occlusive, 24-h, intact and abraded skin).
        - *L(+) lactic acid:* The chemical (0.5 mL of an 88% solution) was slightly irritating to guinea pig skin (semi-occlusive, up to 4 h).
        - *L(+) lactic acid:* The chemical (0.5 mL of an 88% solution) was not irritating to guinea pig skin (occlusive, up to 4 h).
    - HSDB 2006 –
        - In a human skin test, 49 atopic and 56 nonatopic patients received application of 2.5% lactic acid in water. Finn chambers containing 20 µL test solution were fixed on the skin using porous tape for 20 min. No immediate reactions were seen.
    - ECHA 2013 –
        - *L(+) lactic acid* : In a dermal toxicity study, L(+) lactic acid in a face cream at 0.2125% (886 mg/kg/day) was applied topically to female Sprague-Dawley rats (15/group) 5 days/week for 13 weeks. Animals were observed daily and blood and urine were analyzed during weeks 7 and 13 from randomly selected animals. All animals survived to the end of the study. No significant gross observations except minimal skin irritation throughout the study could be attributed to dosing.

Although no measured data were identified for lactide, it was classified as a GHS category 2 skin irritant according to a secondary source. Its surrogate lactic acid was tested to be irritating to the skin at high concentrations. Data on the surrogate support the GHS category 2 classification of lactide.

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

Lactide was assigned a score of Very High for eye irritation/corrosivity based on the classification as a GHS Category 1 eye irritant. GreenScreen™ criteria classify chemicals as a Very High hazard for eye irritation/corrosivity when classified as GHS Category 1 eye irritants and associated with the EU R-Phrase 41 (CPA 2012a). The assignment of this score is supported by data available for the surrogate lactic acid which demonstrated severe irritation when applied to the chicken eye.

- Authoritative and Screening Lists
    - *Authoritative:* not listed in any authoritative lists
    - *Screening:* not listed in any screening lists
- Futerro 2010 –
    - Lactide is classified as a GHA Category 1 eye irritant, H318 – causes serious eye damage.
    - Lactide is associated with the EU Risk Phrase R41- Risk of serious damage to eyes
- Data on surrogate lactic acid –
    - U.S. EPA 2008 (ECHA 2013) –
        - *L(+) lactic acid:* the chemical (0.03 mL of 88% lactic acid in water) was severely

irritating to the chicken eye in a chicken enucleated eye test performed under GLP. According to the EC classification scheme, this material can be considered a R41 (severely irritating to eyes).

- ECHA 2013–
  - *L(+) lactic acid:* the chemical (85%) is irritating to the eyes. No further information was provided.
- HSDB 2006 –
  - The lactic acid's effect on human eyes is similar to that of other acid of moderate strength, causing initial epithelial coagulation on cornea and conjunctiva. Its injurious effect is presumably attributed to its acidity, since lactate ion is a normal and nontoxic constituent of body fluids.

Although no measured data were identified for lactide, it was classified as a GHS category 1 eye irritant according to a secondary source. Its surrogate lactic acid was tested to be severely irritating to the eye at high concentrations. Data on the surrogate support the GHS category 1 classification of lactide.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M or L): *M*
Lactide was assigned a score of Moderate for acute aquatic toxicity based on calculated L/EC_{50} values that fall between 10 and 100 mg/L. Level of confidence was low due to the use of modeled data. GreenScreen™ criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when the acute aquatic toxicity values fall between 10 and 100 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- U.S EPA 2012b –
  - No measured data are available for lactide. Therefore, ECOSAR was used to estimate the aquatic toxicity of this chemical (Appendix C). Lactide has predicted acute aquatic L/EC_{50} values of 31.041 mg/L (fish, 96-hr), 67.023 mg/L (daphnid, 48-hr), and 30.173 mg/L (algae, 96-hr).

Chronic Aquatic Toxicity (CA) Score (vH, H, M or L): *M*
Lactide was assigned a score of Moderate for chronic aquatic toxicity based on calculated ChV values that fall between 1.0 to 10 mg/L. Level of confidence was low due to the use of modeled data. GreenScreen™ criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when the chronic aquatic toxicity vales fall between 1.0 and 10 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- U.S. EPA 2012b –
  - No measured data are available for lactide. Therefore, ECOSAR was used to estimate the chronic toxicity of this chemical (Appendix C). Lactide has predicted chronic aquatic ChV values of 2.515 mg/L (fish), 50.747 mg/L (daphnid), and 6.893 mg/L (algae)

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *M*
Lactide was assigned a score of Moderate for persistence based on it having an estimated half-life in soil of 30 days. Level of confidence was low due to the use of modeled data. GreenScreen™ criteria classify chemicals as a Moderate hazard for persistence when soil half-lives are between 16 and 60 days (CPA 2012a). Although the BIOWIN model predicts that lactide is going to be readily biodegradable, no experimental data are available to demonstrate the biodegradation so the results of the fugacity models were used as the basis for the moderate score for persistence in order to be as protective of the environment as possible.

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- U.S. EPA 2012a –
  - No relevant data could be found for lactide. As a result, EPISuite was used to predict the biodegradability of this chemical (Appendix D). BIOWIN predicted that lactide is readily biodegradable, with primary degradation occurring over a period of days and ultimate degradation occurring over a period of weeks.
  - Fugacity modeling predicts 55.7% of lactide will partition to soil with a half-life of 30 days, 38.2% will partition to water with a half-life of 15 days, and 6.02% will partition to air with a half-life of 114 hours. Based on the modeled data, lactide is expected to persist in the environment as it has half-lives of greater than 30 days in the major environmental compartments.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *vL*
Lactide was assigned a score of vL for bioaccumulation based on the predicted BCF of 5.658 and a predicted Log K_{ow} of 1.65. Level of confidence was low due to the use of modeling. GreenScreen™ criteria classify chemicals as a vL hazard for bioaccumulation when BCFs/BAFs are less than 100 or Log K_{ow} values are less than 4 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- U.S. EPA 2012a –
  - No relevant data could be found for lactide. As a result, EPISuite was used to predict the biodegradability of this chemical (Appendix D). BCFBAF predicted a BCF of 5.658 based on a measured Log K_{ow} of 1.65 for lactide

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M or L): L
Lactide was assigned a score of Low for reactivity based on being of low risk for explosion. GreenScreen™ criteria classify chemicals as a Low hazard for reactivity when stable under normal conditions (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- Futerro 2013 –
  - Lactide is stable under normal operating conditions of storage, handling, and use. This chemical will react with water to form lactic acid.

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

Lactide was assigned a score of Low for flammability. GreenScreen™ criteria classify chemicals as a Low hazard for flammability when the substance is not flammable or combustible (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- Futerro 2013–
  - Lactide is not flammable or combustible.

References

ChemIDplus. 2013a. Entry for Dilactide (CAS #95-96-5). United States National Library of Medicine. Available: http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle=DBMaint&actionHandle=default&nextPage=jsp/chemidheavy/ResultScreen.jsp&ROW_NUM=0&TXTSUPERLISTID=0000095965

ChemIDplus. 2013b. Entry for 1,4-Dioxane-2,5-dione, 3,6-dimethyl-, (3S, 6S) (CAS #4511-42-6). United States National Library of Medicine. Available: http://chem.sis.nlm.nih.gov/chemidplus/ProxyServlet?objectHandle=DBMaint&actionHandle=default&nextPage=jsp/chemidheavy/ResultScreen.jsp&ROW_NUM=0&TXTSUPERLISTID=0004511426

Clary, J.J., V.J. Feron, and J.A. van Vehlthuijsen. 2001. Evaluation of Potential Neurotoxic Effects of Occupational Exposures to (L)-Lactates. Regul. Toxicol. Pharmacol. 33(1):21-28. Abstract available: http://www.ncbi.nlm.nih.gov/pubmed/11259176. Abstract only.

Clean Production Action (CPA). 2011. The GreenScreen™ for Safer Chemicals Version 1.2 Benchmarks. Available: http://www.cleanproduction.org/library/greenScreenv1-2/GreenScreen_v1-2_Benchmarks_REV.pdf

Clean Production Action (CPA). 2012a. The GreenScreen™ for Safer Chemicals Version 1.2 Criteria. Dated: November 2012. Available: http://www.cleanproduction.org/library/GreenScreen_v1_2-2e_CriteriaDetailed_2012_10_10w_all_Lists_vf.pdf

Clean Production Action (CPA). 2012b. List Translator. Dated February 2012. Available: http://www.cleanproduction.org/Greenscreen.ListTranslator.php

Clean Production Action (CPA). 2013. The GreenScreen™ for Safer Chemicals Chemical Hazard Assessment Procedure. Version 1.2 Guidance. Dated September 18, 2013. Available: http://www.cleanproduction.org/library/greenScreenv1-2/GreenScreenv1-2_Guidance_Assessment_Procedure_FINAL_2013_9_18.pdf

D'Amour, F.E. 1934. Effects of Feeding Sodium Bicarbonate or Lactic Acid upon the Sex Ratio in Rats. Science. 79(2038):61-62.

European Chemicals Agency (ECHA). 2013. Entry for lactic acid. Registered substances. Available: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d9206e2-b2f0-4755-e044-00144f67d249/AGGR-1ed2f460-e5ec-4a56-bb2d-8938fec73f37_DISS-9d9206e2-b2f0-4755-e044-00144f67d249.html#AGGR-1ed2f460-e5ec-4a56-bb2d-8938fec73f37

Expert Publishing LLC (ExPub). 2013. Entry for Dilactide (CAS #95-96-5). Available: http://www.expub.com/Members/ChemIdExpertSearchResults.aspx

Futerro. 2010. Safety Data Sheet for L-Lactide (CAS #4511-42-6). Available: http://www.futerro.com/documents/msds_llactide_en.pdf

Futerro. 2013. Entry for Lactide. Available: http://www.futerro.com/products_lactide.html

Grandjean, P. and P.J. Landrigan. 2006. Developmental neurotoxicity of industrial chemicals. Lancet 368:2167-2178. Abstract available: http://www.ncbi.nlm.nih.gov/pubmed/17174709

Hazardous Substances Data Bank (HSDB). 2006. Entry for lactic acid. United States National Library of Medicine. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+50-21-5

Herbert, C.D., H.D. Giles, J.E. Heath, D.B. Hogan, J.P. Modderman, and R.E. Conn. 1999. Toxicity of lactide in dogs after 2 and 13 weeks of daily oral dosing. Food Chem. Toxicol (4):335-342. Abstract available: http://www.ncbi.nlm.nih.gov/pubmed/?term=10418951. Abstract only.

Pharos. 2012. Pharos Chemical and Material Library Entry for Lactide (CAS #4511-42-6; 615-95-2). Available: http://www.pharosproject.net/material/

ToxServices. 2013. SOP 1.37: GreenScreen™ Hazard Assessment. Dated: April 24, 2013.

United States Environmental Protection Agency (U.S. EPA). 2008. Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals. Lactic acid (CAS #50-21-5). Risk Assessment Division. Office of Pollution Prevention and Toxics (OPPT). Accessed through www.expub.com

United States Environmental Protection Agency (U.S. EPA). 2009. Biopesticides Registration Action Document for L-Lactic Acid. Biopesticides and Pollution Prevention Division. Office of Pesticide Programs. Available: http://www.epa.gov/pesticides/chem_search/reg_actions/registration/decision_PC-128929_1-Jun-09.pdf

United States Environmental Protection Agency (U.S. EPA). 2012a. Estimation Programs Interface (EPI) Suite™ Web, v4.11, Washington, DC, USA.

United States Environmental Protection Agency (U.S. EPA). 2012b. ECOSAR v1.11. Washington, D.C, USA.

APPENDIX A: Hazard Benchmark Acronyms (in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(Cr) Corrosion/ Irritation (Skin/ Eye)

(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 GreenScreenTM Score Calculation for Lactide (CAS #4511-42-6; 615-95-2)

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
							S	R *	S	R *	*	*								
Table 2: Chemical Details																				
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	DG	H	vH	*M*	*M*	*M*	*vL*	L	L

Table 3a: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen™ Benchmark Score
Lactide	2

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

Table 6

Chemical Name	Final GreenScreen™ Benchmark Score
Lactide	2

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	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: ECOSAR Modeling Results for Lactide (CAS #4511-42-6; 615-95-2)

ECOSAR Version 1.11 Results Page

SMILES : O=C(OC(C(=O)O1)C)C1C
CHEM : 1,4-Dioxane-2,5-dione, 3,6-dimethyl-
CAS Num: 000095-96-5
ChemID1:
MOL FOR: C6 H8 O4
MOL WT : 144.13
Log Kow: 1.645 (EPISuite Kowwin v1.68 Estimate)
Log Kow: (User Entered)
Log Kow: (PhysProp DB exp value - for comparison only)
Melt Pt: (User Entered for Wat Sol estimate)
Melt Pt: 117.50 (deg C, PhysProp DB exp value for Wat Sol est)
Wat Sol: 930.3 (mg/L, EPISuite WSKowwin v1.43 Estimate)
Wat Sol: (User Entered)
Wat Sol: (PhysProp DB exp value)

Values used to Generate ECOSAR Profile

Log Kow: 1.645 (EPISuite Kowwin v1.68 Estimate)
Wat Sol: 930.3 (mg/L, EPISuite WSKowwin v1.43 Estimate)

ECOSAR v1.11 Class-specific Estimations

Esters

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Esters	: Fish	96-hr	LC50	31.041
Esters	: Daphnid	48-hr	LC50	67.023
Esters	: Green Algae	96-hr	EC50	30.173
Esters	: Fish		ChV	2.515
Esters	: Daphnid		ChV	50.747
Esters	: Green Algae		ChV	6.893
Esters	: Fish (SW)	96-hr	LC50	48.258
Esters	: Mysid	96-hr	LC50	56.527
Esters	: Fish (SW)		ChV	6.490
Esters	: Mysid (SW)		ChV	8568.570 *
Esters	: Earthworm	14-day	LC50	2444.961 *

Neutral Organic SAR	: Fish	96-hr	LC50	246.499
(Baseline Toxicity)	: Daphnid	48-hr	LC50	135.455
	: Green Algae	96-hr	EC50	88.126
	: Fish		ChV	23.182
	: Daphnid		ChV	12.059
	: Green Algae		ChV	21.455

Note: * = asterisk designates: 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.

Class Specific LogKow Cut-Offs

If the log Kow of the chemical is greater than the endpoint specific cut-offs presented below, then no effects at saturation are expected for those endpoints.

Esters:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogKow: 6.0 (Earthworm LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)

Baseline Toxicity SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)

APPENDIX D: EPISuite Modeling Results for Lactide (CAS #4511-42-6; 615-95-2)

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): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.68 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): 0.000157 (Modified Grain method)
VP (Pa, 25 deg C) : 0.0209 (Modified Grain method)
MP (exp database): 117.5 deg C
BP (exp database): 142 @ 8 mm Hg deg C
Subcooled liquid VP: 0.00129 mm Hg (25 deg C, Mod-Grain method)
: 0.172 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 3165
log Kow used: 1.65 (estimated)
no-melting pt equation used

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: 9.407E-009 atm-m3/mole (9.532E-004 Pa-m3/mole)
VP: 0.000157 mm Hg (source: MPBPVP)

WS: 3.17E+003 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 1.65 (KowWin est)
Log Kaw used: -3.302 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 4.952
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) : 0.9965
Biowin6 (MITI Non-Linear Model): 0.9542
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): 0.172 Pa (0.00129 mm Hg)
Log Koa (Koawin est): 4.952
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 1.74E-005
Octanol/air (Koa) model: 2.2E-008
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.00063
Mackay model : 0.00139
Octanol/air (Koa) model: 1.76E-006

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):
0.00101 (Junge-Pankow, Mackay avg)
1.76E-006 (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 : 50.88 L/kg (Kow method)
Log Koc: 1.707 (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 = 0.753 (BCF = 5.658 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -2.4066 days (HL = 0.003921 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.219 (BCF = 1.656)
Log BAF Arnot-Gobas method (upper trophic) = 0.219 (BAF = 1.656)
log Kow used: 1.65 (estimated)

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: 2.69 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.92 percent
Total to Air: 0.68 percent
(using 10000 hr Bio P,A,S)

Removal In Wastewater Treatment:
Total removal: 92.22 percent
Total biodegradation: 91.68 percent
Total sludge adsorption: 0.43 percent
Total to Air: 0.11 percent
(using Biowin/EPA draft method)

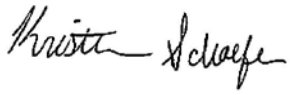
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.02	114	1000
Water	38.2	360	1000
Soil	55.7	720	1000
Sediment	0.086	3.24e+003	0

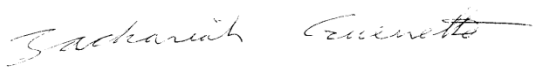
Persistence Time: 381 hr

Authorized Reviewers

Lactide GreenScreen™ Evaluation Prepared By:

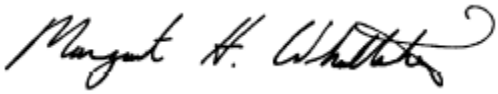


Kristen Schaefer, M.F.S.
Associate Toxicologist
ToxServices LLC



Zachariah Guerrette, Ph.D.
Toxicologist
ToxServices LLC

Lactide GreenScreen™ Evaluation QC'd By:



Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.S.B., E.R.T., D.A.B.T.
Managing Director and Chief Toxicologist
ToxServices LLC