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Administrator
US Environmental Protection Agency
Attention: Chemical Right to Know Program
MERRIFIELD,VA 22116
USA

Gorinchem, January 4, 2002

Re : Chemical Right to Know Program

Dear administrator,

Herewith I submit, on behalf of PURAC America Inc., the proposed test plan together with the robust summary and the data on the SIDS endpoints for the chemical lactic acid, CAS number 50-21-5 (79-33-4). You will find all information in the ZIP file attached to this mail. The content of the ZIP file is given below. I understand that there will be a 120 days review period for the test plan. I trust that all comments received by the EPA will be forwarded to PURAC, for my attention.

It is good to mention that PURAC America Inc. was committed to send in data on CAS number 50-21-5, which is the racemic form of lactic acid. However, my company and most other suppliers of lactic acid, only manufacture the natural form of lactic acid, L(+) lactic acid. Most data available in public literature are about the L(+) form and most studies done have been performed with L(+) lactic acid. According to us, it made sense therefor to base the files on L(+) lactic acid (CAS# 79-33-4).

L(+) Lactic Acid is an organic acid, which is an essential element of human metabolism. Each human being metabolises between 125 and 150 grams of L(+) Lactic Acid daily. Therefor risk issues are not to be expected.

L(+) Lactic Acid has a GRAS status which can be found in 21 CFR § 184.1061. L(+) Lactic Acid is also included in the TSCA list.

L(+) Lactic Acid has been approved as a food additive (E 270), without restrictions under European legislation.

Please feel free to contact me (at telephone +31 183 695730 or e-mail t.van.dongen@purac.com) in case you have questions concerning this application.

Yours sincerely

Ton van Dongen
Corporate QA&RA Manager

Encl. A zip file [HPV 79_33_4] with:

- This letter [letter right to know 50-21-5.doc]
- Robust summary and test plan [hpv_test plan justification & test plan 50-21-5.doc]
- MS-Word on L(+) Lactic Acid [HPV data 50_21_5.doc]

AR201-13462A

LACTIC ACID

CAS # 50-21-5
HPV CHEMICAL # 50215

TEST PLAN JUSTIFICATION

TEST PLAN

SUBMITTED JANUARY 3rd 2002.

SPONSORED BY:
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PREPARED BY:

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1. TEST PLAN JUSTIFICATION FOR LACTIC ACID (CAS# 50-21-5)

It is good to mention that PURAC America Inc. was committed to send in data on CAS number 50-21-5, which is the racemic form of lactic acid. However, PURAC and most other suppliers of lactic acid, only manufacture the natural form of lactic acid, L(+) lactic acid. Most data available in public literature are about the L(+) form only and most studies done have been performed with L(+) lactic acid. Therefor it made sense to base the files on L(+) lactic acid (CAS# 79-33-4). This document has been written to summarise the findings of the robust summary for L(+) lactic acid, to describe other relevant literature and to explain why no additional testing is proposed for L(+) Lactic Acid.

- Introduction

Lactic acid (2-Hydroxypropionic acid) was discovered in 1780 by the Swedish chemist Scheele. L(+) lactic acid is an organic acid which is an essential part of human metabolism. Also many different animals and micro-organisms need L(+) lactic acid in their metabolism.

L(+) lactic acid is an organic acid with a long history in food. E.g. in fruits it is formed through fermentation. Nowadays, L(+) lactic acid and its derivatives are maily used in the food industry e.g. for preservation and flavouring purposes. L(+) lactic acid has a GRAS status and it has a European food additive approval (E 270). L(+) lactic acid has been approved in many other countries as a food additive.

On top of that, there is an increased number of applications in the pharmaceutical, cosmetic and chemical industry. The world production of L(+) lactic acid is around 100,000 tons per year. Major part of this volume is manufactured by fermentation of various carbohydrate sources and subsequent down stream purification. Some lactic acid (mainly the racemic form) is manufactured by synthesis and purification.

Every human being "produces" and metabolises daily about 125 - 150 grams of L(+) lactic acid. Relative contribution of the L(+) lactic acid consumed to the human metabolism is relatively very low. Consumption of 50,000 tons of L(+) lactic acid (half of the global production) across the USA would lead to an additional L(+) lactic acid intake / metabolism of 550 micrograms / person / day, being 0,45% of the normal daily metabolism.

- Physical - chemical properties

L(+) lactic acid is a clear to slightly yellowish liquid, typically supplied to formulators in a 88 - 92% concentration. The physical and chemical properties of L(+) lactic acid have been well described. The boiling point and melting point, vapour pressure, water solubility and partition coefficient are very well known. Much information on lactic acid e.g. can be found in the book "Lactic acid, properties and chemistry of lactic acid and derivatives" by C.H. Holten (1971).

- Environmental fate

Photodegradation

The photochemical oxidation of Lactic Acid is discussed in the handbook by C.H. Holten, mentioned above. Berthelot and Gaudechon, who irradiated calcium lactate and ethyl lactate, made the first observation that lactic acid is photosensitive in 1910. They observed decomposition with the formation of a gas containing carbon monoxide, carbon dioxide, hydrogen and methane.

Stability in water

From the robust summary it is clear that lactic acid in an aqueous environment will have a very high stability (between 79 and 98 years).

Transport between compartments

If discharged into water, L(+) lactic acid will stay predominantly in the water compartment. As L(+) lactic acid is not volatile and as it has a high biodegradation rate, transport between environmental compartments (air and soil / water) is no issue.

Biodegradation

The biodegradability of L(+) lactic acid was examined using the Biological Oxygen Demand (BOD) and the Chemical Oxygen Demand (COD). Testing was done according EC test guidelines and OECD GLP principles.
The BOD_5 was found to be 0.45 mg O_2/mg and the BOD_{20} was found to be 0.60 mg O_2/mg. The COD was 0.90 mg O_2/mg. These figures show a degradation of 50% after 5 days and 67% after 20 days.
Thus L(+) lactic acid is highly biodegradable. L(+) lactic acid is widely recognised as being readily biodegraded in the environment as it is both a nutrient and a metabolite for microbes. Accordingly, L(+) lactic acid is not expected to biopersist or bioaccumilate in the environment.

- Ecotoxicity

Acute toxicity to aquatic plants

One study exhibits the very low toxicity of L(+) lactic acid in Algae Selenastrum Capricornutum, as the Observed No Effect Concentration was found to be 1.9 g/l

Aquatic toxicity to invertebrates

In two other studies, L(+) lactic acid also exhibits very low toxicity to aquatic organisms. Two studies have been done to establish the toxicity of L(+) lactic acid to Daphnia Magna. Both studies covered a period of up to 48 hours. The 48 hours No Observed Effect Concentration ranged from 180 mg/L to 320 mg/L.

Acute toxicity to fish

Three studies have been done to establish the toxicity of L(+) lactic acid in Salmo Gairdneri (rainbow trout), Lepomis Macrochirus (bluegill sunfish) and to Brachydanio Rerio. These studies covered a period of up to 96 hours. The No Observed Effect Concentration ranged from 56 mg/l to 320 mg/l.

- Health Endpoints

Acute Oral Toxicity

As mentioned, L(+) lactic acid is an essential link in the mammalian metabolism. Therefor it will be clear that L(+) lactic acid is practically non-toxic. This is also shown by the LD_{50} values of L(+) lactic acid obtained after various routes of administration in mammals.

The oral LD50 was found to be a little below 5 grams / kg bodyweight in male rats and a little over 3,5 grams/kg body weight in female rats. Several non-critical symptoms were recorded at a dose level of 5 g/kg bodyweight.

Acute Dermal Toxicity

In a prior test conducted in 1986, corrosive effects were observed in albino rabbits exposed to 88% L(+) lactic acid. However, it is well established that for many compounds the skin of the rabbit is substantially more permeable to topically applied compounds than is the human skin and that permeability is, in turn, directly related to potential irritive effects. Because of that TNO (Dutch Institute for Applied Science) concluded that the test using albino rabbits did not adequately predict the probable effect of 88% unbuffered L(+) lactic acid on human skin and that re-testing with a more representative model was indicated. A number of comparative studies *in vivo* on percutaneous absorption have shown the skin of the pig to be most relevant to the skin of man. In this regard it is worth to mention that both the 1981 and 1992 versions of OECD guideline 404 state that while the albino rabbit is the preferred test animal, "several mammalian species may be used". The guideline leaves the choice of species to the researcher's sound scientific judgement.
Accordingly, TNO selected pigs as a more appropriate and representative animal model for re-testing of L(+) lactic acid. In pigs L(+) lactic acid did not give any serious skin irritation.

On basis of the test results provided, the US-DOT (Department of Transport) came to the following conclusion: "Based on the definition of "corrosive materials" at 49 CFR 173.136, test criteria to determine the packing group of class 8 material at 49 CFR 173.137, and test data and other information submitted, it is the DOT's opinion that lactic acid as tested is not a corrosive material.

In-vitro genotoxicity

An Ames test was done to establish the in-vitro genotoxicity. Results were negative. Also, the nature of L(+) lactic acid (human metabolite) does make additional testing not necessary.

Repeated dose toxicity

Four studies have been reported in the robust summary about repeated dose toxicity, three in rats and one in hamsters.

- 90 days - rat - 4ml lactic acid 10% on 20 g of meal
No differences in appearance, gross observations at necropsy, or organ weights were observed between the test and control animals. Changes in blood carbon dioxide were slight.

- 13 weeks - rat - 886 mg/kg bodyweight.
There were no significant gross observations, with the exemption of mild skin irritation. Absolute brain weight and kidney-to-body weight rations were increased for test animals. No lesions were seen observed at necropsy or at microscopic examination

- 14 weeks - hamster - water containing up to 0.05% lactic acid ad libitum
Three groups showed same growth and health..

- 13 weeks - rats - 0,3 to 5% calcium lactate in food.
A 10% decrease in body weight gain. All animals survived, some haematological and biochemical parameters changed, but no severe lesions were found in microscopic examination.

Reproductive toxicity / In-vivo genotoxicity / Developmental toxicity

It has been mentioned that L(+) lactic acid is an essential part of the human metabolism. Every human being makes and metabolises about 125 - 150 grams of L(+) lactic acid each

day. Although studies have not been done to investigate reproductive toxicity, in-vivo genotoxicity or developmental toxicity, it will be clear that L(+) lactic acid has such a low potential risk (~ zero) that studies will not be needed.

- Conclusion

The information given in the robust summary will be adequate to establish the environmental fate and toxicity of L(+) lactic acid. Therefor no additional testing will be needed.

2. TEST PLAN FOR L(+) LACTIC ACID (CAS# 50-21-5)

	Information provided?	Data according GLP or OECD	Data Acceptable?	Additional tests required?
	Yes / No	Yes / No	Yes / No	Yes / No
Physical Chemical Data				
Melting Point	Yes	No	Yes	No
Boiling Point	Yes	No	Yes	No
Vapor Pressure	Yes	No	Yes	No
Partition Coefficient	Yes	No	Yes	No
Water Solubility	Yes	No	Yes	No
Environmental Fate				
Photodegradation	Yes	No	Yes	No
Stability in water	Yes	Yes	Yes	No
Transport between compartments	Yes	Yes	Yes	No
Biodegradation	Yes	Yes	Yes	No
Ecotoxicity				
Acute toxicity to aquatic plants	Yes	Yes	Yes	No
Acute toxicity to aquatic invertebrates	Yes	Yes	Yes	No
Acute toxicity to fish	Yes	Yes	Yes	No
Health endpoints				
Acute toxicity to mamals	Yes	Yes	Yes	No
Genetic toxicity in vivo	Yes	No	Yes	No
Genetic toxicity in vitro	Yes	No	Yes	No
Repeat dose toxicty	Yes	Yes	Yes	No
Reproductive toxicity	Yes	No	Yes	No
Developmental toxicity	Yes	Yes	Yes	No

AR201-13462B

HPV Data Set

LACTIC ACID

CAS # 50-21-5

Dossier number 50215

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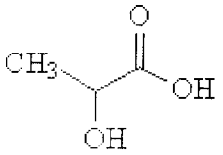
Substance information

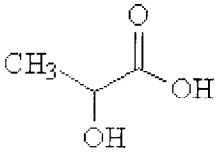
CAS No.	50-21-57
EINECS Name:	lactic acid
EC No.	200-018-0
TSCA Name:	Propanoic acid, 2-hydroxy-, (2S)-
Molecular Formula	C3H6O3



IUPAC Name:	LACTIC ACID
Mol. Weight:	90
Physical status:	liquid or white crystals
Colour:	colourless to slightly yellow
Odour:	nearly odourless

Most of the lactic acid nowadays is supplied in the L(+) form, the natural form. PURAC only manufacturers the L(+) form.
Substance information for the L(+) lactic acid is as follows:

CAS No.	79-33-4
EINECS Name:	L(+) lactic acid
EC No.	201-196-2
TSCA Name:	Propanoic acid, 2-hydroxy-, (2S)-
Molecular Formula	C3H6O3



IUPAC Name:	L(+) LACTIC ACID
Mol. Weight:	90
Physical status:	liquid or white crystals
Colour:	colourless to slightly yellow
Odour:	nearly odourless

This HPV data file typically contains information about L(+) lactic acid.

Chapter 1 Physico-chemical Data

- ***Melting Point***

Value:	≤ 54 degree C
Decomposition:	no at < 110 degree C
Sublimation:	no
Method:	other
GLP:	no data
Test substance:	100% crystalline pure product used

- **Boiling Point / Vapour pressure**

Boiling point:	ca. 258 degree C at 1000 hPa
Vapour pressure:	ca. .0041 hPa at 20 degree C
Decomposition:	yes
Method:	other
GLP:	no data
Remark:	solutions can polymerise on boiling

It is not possible to determine this value very accurate, because lactic acid tends to polymerise by a polycondensation reaction.
The boiling point of lactic acid at difference vapour pressures according to

- Aspen Database
- PURAC In-house Pure compound database

Table Boiling points of lactic acid at different pressures (Aspen Database)

Pressure (mbar)	Boiling temperature (°C)
1	79.6
5	101.9
10	112.8
50	141.8
100	156.2
200	172.1
400	189.8
600	201.0
800	209.4
1013	216.6

The vapour pressures of lactic acid as a function of the boiling temperature according to the Aspen formula (PLXANT).

$$PLXANT = e^{C1 + \frac{C2}{C3+T} + C4*T + C5*\ln T + C6*T^{C7}}$$

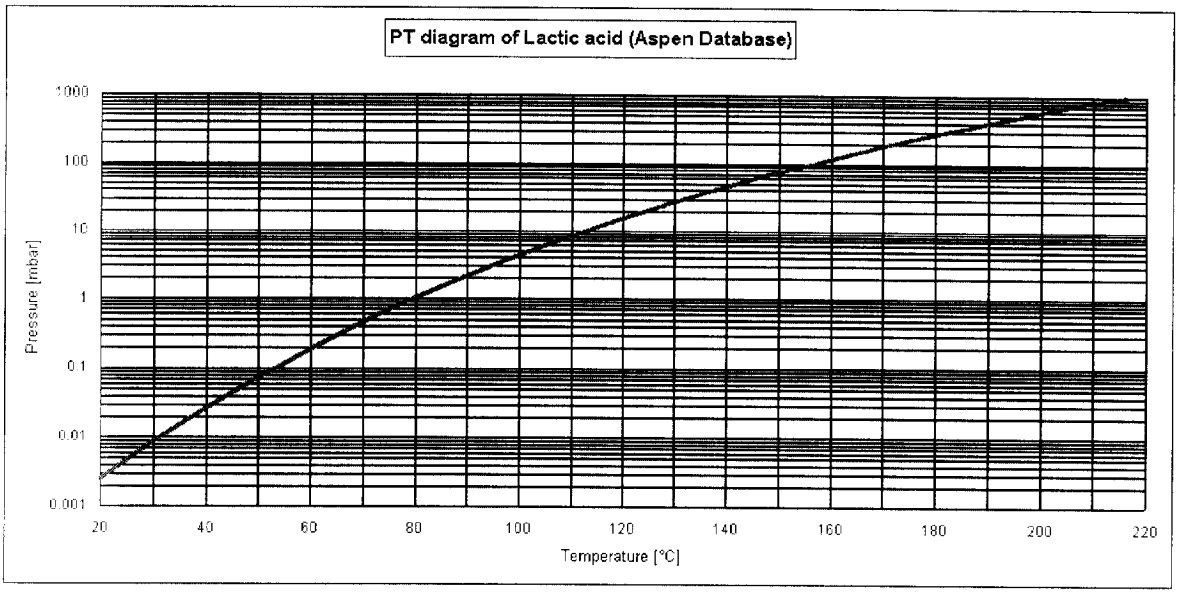
: Vapour pressure (N/m^2 or Pa)

PLXANT

C1, C2 C3, C4, C5, C6, C7 : Regression coefficients for chemical compound

T : Boiling temperature (K)

Figure Vapour Pressure diagram



The regression coefficients are:

C1 = 225.19 C5 = -28.816

C2 = -18757 C6 = 0.000012998

C3 = 0 C7 = 2

C4 = 0

G.P.v.Lieshout measured the vapour pressure of lactic acid between 0 and 180 °C.

Table Boiling points of lactic acid at different pressures

Temperature (°C)	Vapour Pressure (mbar)
0	0.0005
10	0.0015
20	0.0041
30	0.0107
40	0.0258
50	0.0588
60	0.1273
70	0.2629
80	0.5198

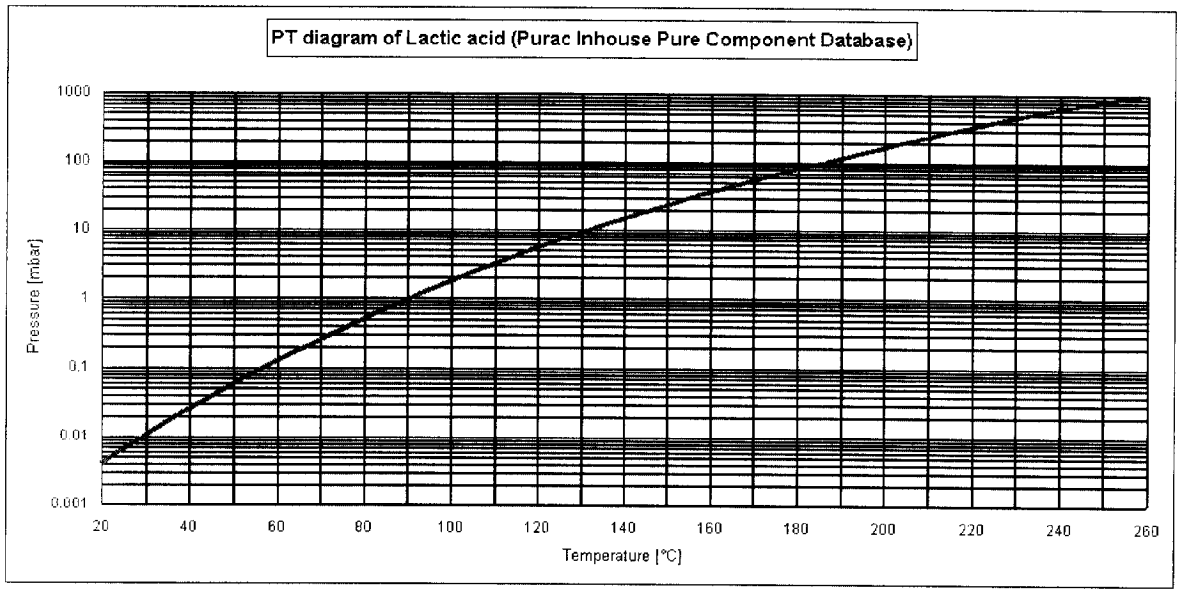
90	0.9877
100	1.8093
110	3.2042
120	5.5004
130	9.1736
140	14.8959
150	23.5938
160	36.5163
170	55.3114
180	82.1111

The vapour pressures of lactic acid as a function of the boiling temperature were fitted with the Aspen formula (PLXANT). The estimated atmospheric boiling point is about 258 °C.

$$PLXANT = e^{C1 + \frac{C2}{C3+T} + C4*T + C5*\ln T + C6*T^{C7}}$$

PLXANT : Vapour pressure (N/m^2 or Pa)

C1, C2 C3, C4, C5, C6, C7 : Regression coefficients for chemical compound



: Boiling temperature (K)

Figure: Vapour Pressure diagram

The regression coefficients are:

C1 = 32.4649	C5 = -0.376037
C2 = -8835.5	C6 = 0
C3 = 0	C7 = 0
C4 = -0.003654	

- **Density**

Type:	density
Value:	>= 1.2255 g/cm³ at 20 degree C
Method:	other
GLP:	yes
Test substance:	Lactic acid 80%

Holten describes the liquid density of lactic acid solutions in water.
Table Liquid Densities of aqueous lactic acid solutions at different temperatures.

Concentration (wt%)	Temperature (°C)										
	0	10	20	30	40	50	60	70	80	90	100
0	1.0004	0.9997	0.9979	0.9953	0.9919	0.9878	0.9831	0.9778	0.9720	0.9658	0.9591
10	1.0269	1.0251	1.0223	1.0188	1.0145	1.0097	1.0042	0.9983	0.9919	0.9851	0.9779
20	1.0535	1.0505	1.0468	1.0424	1.0373	1.0317	1.0256	1.0190	1.0120	1.0047	0.9970
30	1.0802	1.0762	1.0715	1.0662	1.0604	1.0540	1.0472	1.0400	1.0325	1.0246	1.0164
40	1.1069	1.1019	1.0964	1.0902	1.0836	1.0766	1.0692	1.0614	1.0533	1.0449	1.0363
50	1.1333	1.1275	1.1211	1.1142	1.1069	1.0992	1.0912	1.0829	1.0743	1.0655	1.0564
60	1.1591	1.1524	1.1453	1.1377	1.1299	1.1216	1.1131	1.1043	1.0953	1.0861	1.0766
70	1.1835	1.1762	1.1685	1.1604	1.1521	1.1434	1.1345	1.1254	1.1160	1.1065	1.0967
80	1.2061	1.1983	1.1902	1.1818	1.1731	1.1642	1.1550	1.1456	1.1360	1.1263	1.1163
90	1.2263	1.2183	1.2100	1.2014	1.1925	1.1834	1.1741	1.1646	1.1550	1.1451	1.1351
95	1.2354	1.2274	1.2190	1.2104	1.2015	1.1924	1.1831	1.1736	1.1639	1.1541	1.1441
100	1.2438	1.2357	1.2274	1.2188	1.2099	1.2008	1.1916	1.1821	1.1725	1.1627	1.1527

Liquid Density of <u>pure lactic acid</u>

The liquid density of pure lactic acid at difference temperatures according to:

- Aspen Database
- PURAC In-house Pure Component Database

Table Densities of lactic acid at different temperatures (ASPEN Database)

Temperature (°C)	Density (g/ml)
20	1.2255
30	1.2163
40	1.2069
50	1.1974
60	1.1878
70	1.1780
80	1.1681
90	1.1580
100	1.1478
110	1.1374
120	1.1268
130	1.1160
140	1.1051
150	1.0939
160	1.0825

The liquid densities of lactic acid as a function of the temperature according to the Aspen equation for liquid density (DNLDIP):

$$DNLDIP = \frac{C1}{C2^{1+(1-\frac{T}{C3})^{C4}}}$$

DNLDIP : Liquid density (kmole/m^3)
C1, C2 C4 : Regression coefficients for chemical compound
C3 : Critical temperature (K)
T : Temperature (K)
The regression coefficients are:
C1 = 0.9798 C3 = 675
C2 = 0.24593 C4 = 0.2333

Liquid density diagram

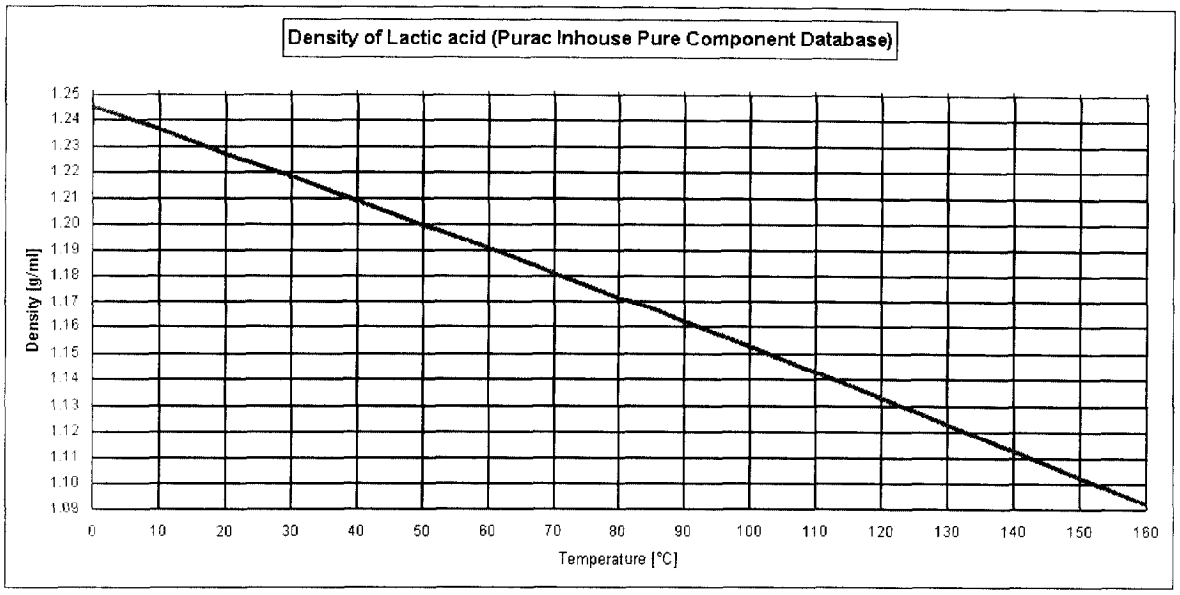


Table Densities of lactic acid at different temperatures (Purac In-house Pure Component Database)

Temperature (°C)	Density (g/ml)
0	1.2453
10	1.2364
20	1.2274
30	1.2183
40	1.2092
50	1.2000
60	1.1907
70	1.1813
80	1.1719
90	1.1623
100	1.1527
110	1.1429
120	1.1330
130	1.1231
140	1.1130
150	1.1028
160	1.0924

The liquid densities of lactic acid as a function of the temperature according to the Aspen equation for liquid density (DNLDIP):

$$DNLDIP = \frac{C1}{C2^{1+(1-\frac{T}{C3})^{C4}}}$$

DNLDIP : Liquid density (kmole/m^3)

C1, C2 C4 : Regression coefficients for chemical compound
C3 : Critical temperature (K)
T : Temperature (K)
The regression coefficients are:
C1 = 1.61248 C3 = 729.9
C2 = 0.314479 C4 = 0.328317

- ***Partition Coefficient***

Partition Coeff.: octanol-water
log Pow: ca. -.62 at 20 degree C
Method: OECD Guide-line 117 "Partition Coefficient (n-octanol/water), HPLC Method"
Year: 1987
GLP: yes

- ***Solubility in water***

Value: ca. 100 vol% at 25 degree C
pH value: ca. 1.2
pKa: 3.68 at 25 degree C
Descr.: of very high solubility
Method: other
GLP: no data
Deg. product: not measured
Stable: yes
Remark: completely soluble at 25 degrees C

J.v.Krieken determined the phase diagram of lactic acid/ water. Due to practical problems the diagram wasn't completed, but the missing part was extrapolated.

Table Solubility of monomeric lactic acid in water

Temperature (°C)	Lactic acid (wt%)
-20	65.9
-15	68.8
-10	71.5
-5	74.2
0	76.7
5	78.6
10	81.3
15	83.5
20	86.1
25	87.6
35	92.7
40	95.1

Table Freezing point data of monomeric lactic acid in water

Temperature (°C)	Lactic acid (wt%)

0	0
-5	18.6
-10	32.5
-15	41.9
-21	51.7

The eutectic point of lactic acid/water was calculated by extrapolation and is ca. 61.7 wt% lactic acid and -27.1 °C.

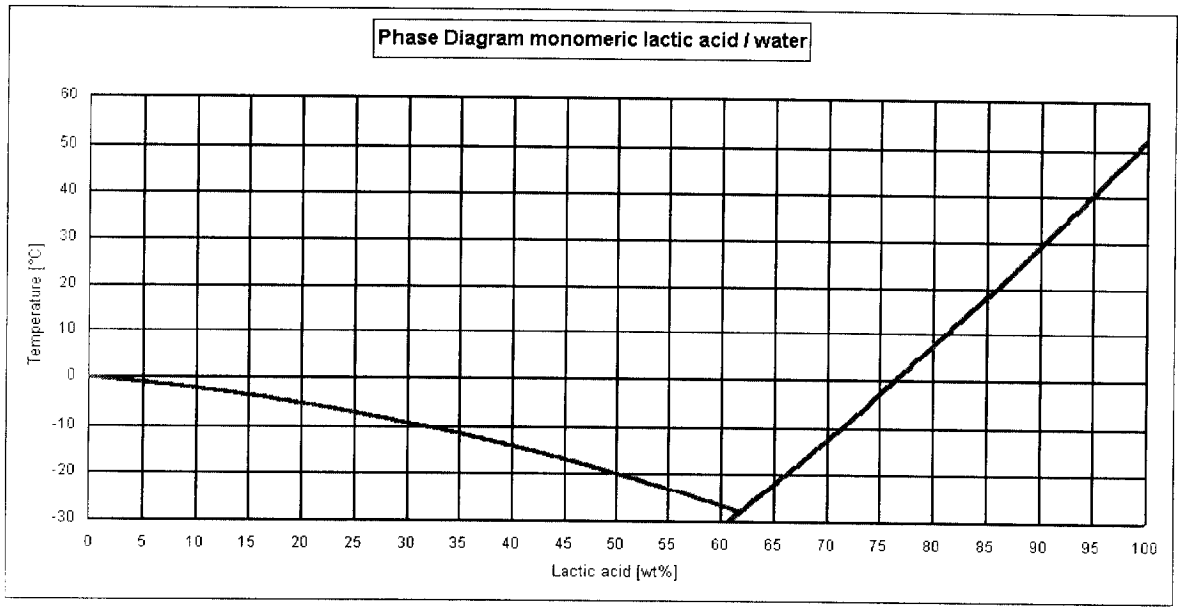


Figure Phase Diagram

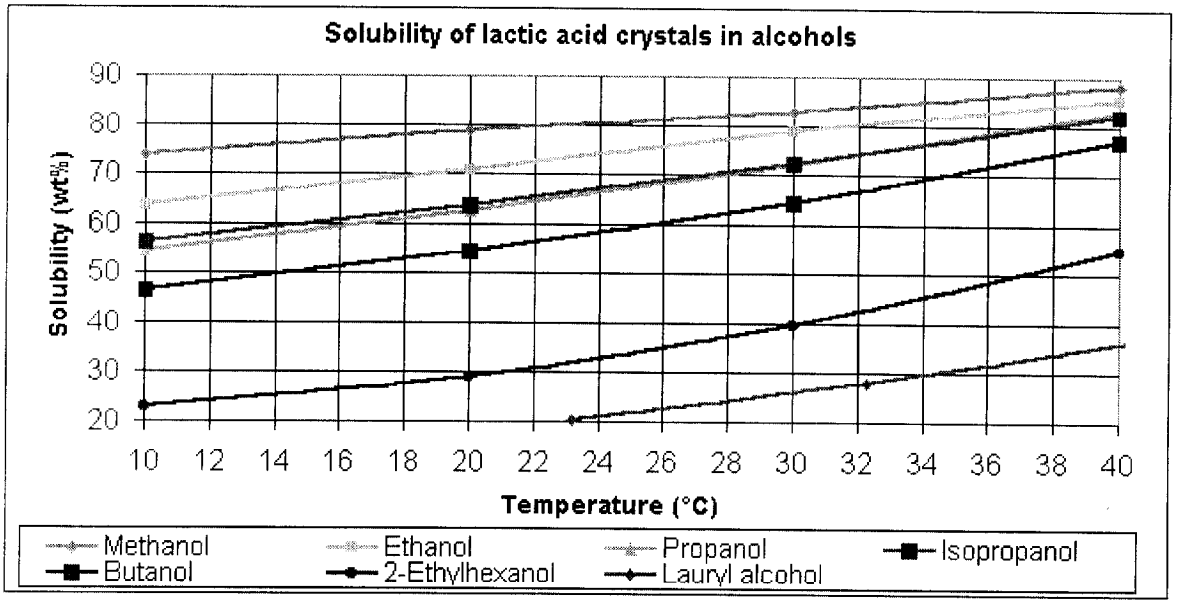
Solubility of lactic acid in other solvents

J.v. Krieken investigated the solubility of pure lactic acid in a range of solvents by stirring the specific solvent with an excess of (S)-lactic acid crystals at a specific temperature. After separation of the solids from the liquid, the clear liquid was analysed on free acidity.

Table solubility of lactic acid in a range of solvents

Solvent	Solubility (wt%) of solution			
	10°C	20°C	30°C	40°C
Methanol	73.8	78.6	82.8	88.1
Ethanol	63.6	70.9	78.7	85.2
1-Propanol	54.5	62.4	71.7	82.7
2-Propanol	56.1	63.4	72.2	82.2
1-Butanol	46.3	54.5	64.3	77.1
2-Ethyl-1-hexanol	22.9	29.0	39.6	54.9
Cyclohexane				0.04
Hexane	< 0.01	< 0.01	< 0.01	0.02

Toluene	0.06	0.11	0.24	0.50
Ethyl lactate	37.0	45.9	57.2	72.8
Butyl lactate	27.7	35.7	47.3	64.8
2-Ethylhexyl lactate	15.5	20.9	30.9	46.7
Ethyl acetate	27.1	39.9	56.2	72.9
Diethyl ether	23.8	38.7	59.8	
Diisopropyl ether	6.4	9.2	15.9	44.4
Tetrahydrofuran	58.4	65.1	72.4	82.9
Dichloromethane	0.59	1.02	2.7	
Chloroform	0.31	0.67	1.67	59.7
2-Butanone	40.7	52.9	67.3	81.6
Acetone	53.4	61.4	71.5	82.9



- ***Viscosity***

Test type: other: ASPEN database ; PURAC internal
Value: ca. 53.52 mPa s (dynamic) at 20 degree C

The liquid viscosity of lactic acid at difference temperatures according to

- Aspen Database
- PURAC In-house Pure Component Database

The liquid viscosity of aqueous lactic acid solutions in water

- 0 - 88 wt% of Lactic Acid
- 90 - 110 wt% Lactic Acid

Table Viscosity of lactic acid at different temperatures (Aspen Database)

Temperature (°C)	Viscosity (cP)
20	53.52
30	33.26
40	21.29
50	14.01
60	9.44
70	6.51
80	4.59
90	3.29
100	2.40
110	1.78
120	1.34
130	1.03
140	0.79
150	0.62
160	0.49

The liquid viscosity of lactic acid as a function of the temperature according to the Aspen equation for liquid viscosity (MULDIP):

$$MULDIP = e^{C1 + \frac{C2}{T} + C3 * \ln T + C4 * T^{C5}}$$

MULDIP : Liquid viscosity ($N*s/m^2$ or Pa.s)
C1, C2 C3, C4, C5 : Regression coefficients for chemical compound
T : Temperature (K)

The regression coefficients are:
C1 = -14.403
C2 = 4097.9
C3 = -0.4407
C4 = 0
C5 = 0

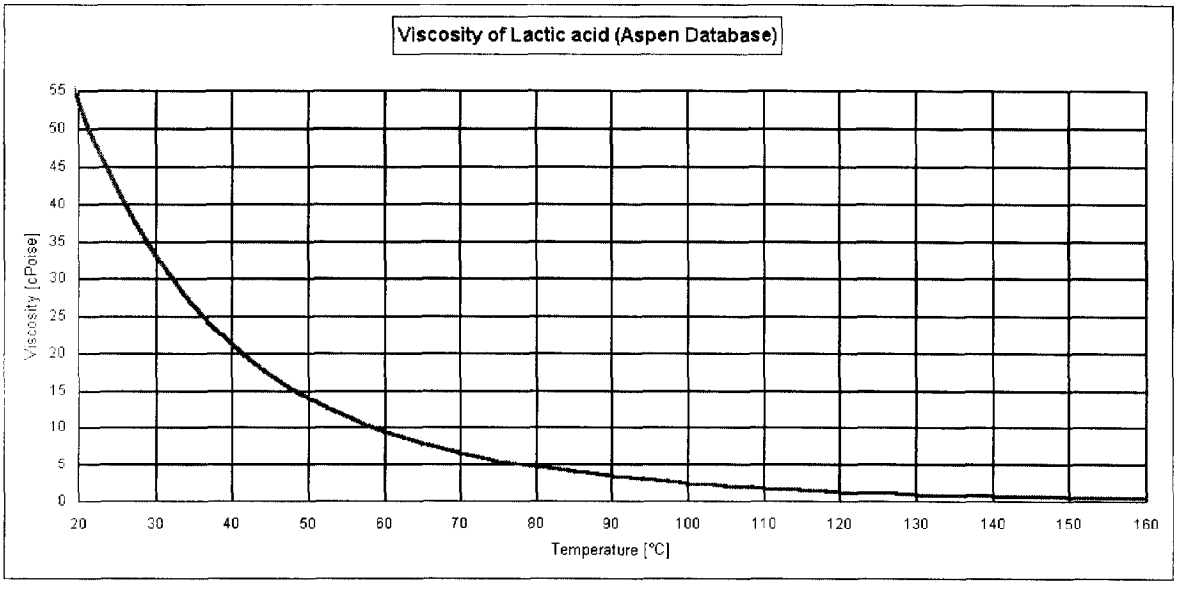


Figure: Liquid Viscosity diagram

Table 12 Viscosity of lactic acid at different temperatures (Purac In-house Pure Component Database) [2]

Temperature (°C)	Viscosity (cP)
20	1342.33
30	579.14
40	280.59
50	150.73
60	88.80
70	56.81
80	39.14
90	28.83
100	22.54

The liquid viscosity of lactic acid as a function of the temperature according to the Aspen equation for liquid viscosity (MULDIP):

MULDIP: Liquid viscosity ($N*s/m^2$ or Pa.s)
C1, C2, C3, C4, C5: Regression coefficients for chemical compound
T: Temperature (K)

The regression coefficients are:

C1: 421.094
C2: 25091.4
C3: 59.1119
C4: 0
C5: 0

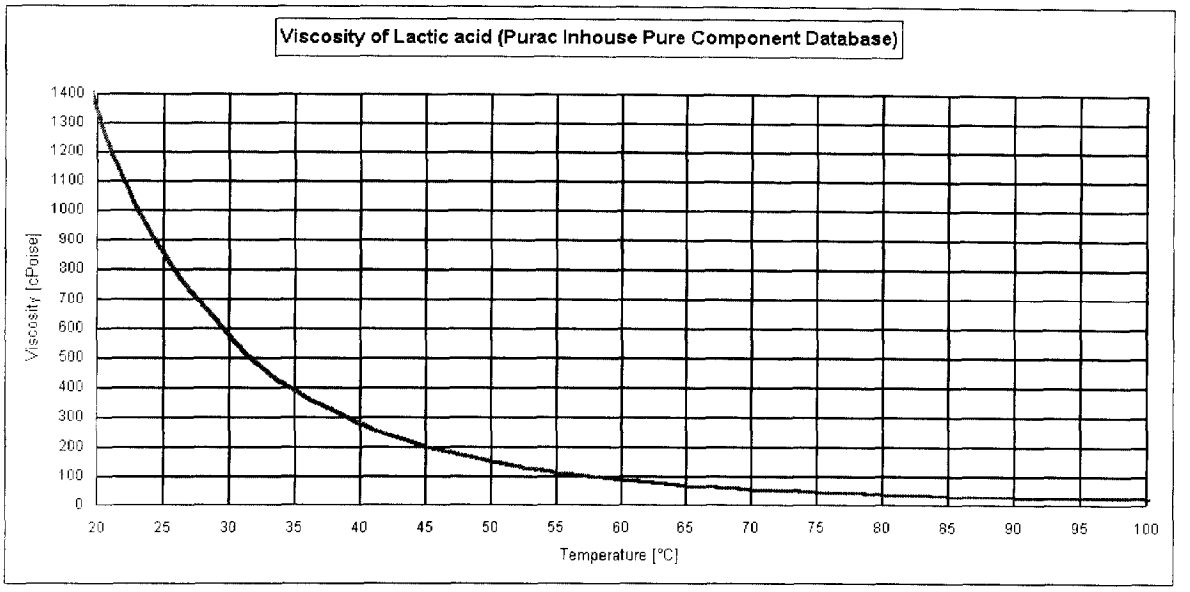


Figure: Liquid Viscosity diagram

References Chapter 1: Physico chemical data

- National Chemical Inventories
  Coden NCINF5
  ISSN: 1089-6279

- Handbook of Chemistry and Physics
  WEAST
  66th Edition

- ASPEN database

- PURAC internal databank

Chapter 2 Environmental Fate and Pathways

- ***Photodegradation***

The photochemical oxidisation of lactic acid is discussed in "Lactic acid properties and chemistry of lactic acid and derivatives by C.H. Holten (1971)". The first observation that lactic acid is photosensitive was made in 1910 by Berthelot and Gaudechon, who irradiated calcium lactate and ethyl lactate with ultraviolet rays. They observed decomposition with the formation of gas containing carbon monoxide, carbon dioxide, hydrogen and methane.

- ***Stability in Water***

Lactic Acid (88% and 60% aqueous solutions) were investigated.
"The kinetics of degradation of Lactic Acid was done at elevated temperature, since the decomposition rates of lactic acid, (..) were too slow to obtain kinetic data within reasonable time. At the condition studied (25, 40, 80 and 120 degrees centigrade) the decompositions of these compounds followed apparent first order kinetics because the mean correlation coefficient was above 0.980.
Lactic acid was very stable in aqueous solutions at 80 degrees centigrade (less than 30% decomposition after 175 at 80 degrees) and degradation was not different when combined with the various excipients tested. The shelf lives determined for lactic acid ranged from 79 years when combined with isopropyl palmitate to 98 years when combined with sorbic acid.

- ***Transport between Environmental Compartments***

Type: other: see free texts RM.
Remark: Lactic acid is not volatile and it has a high biodegradation rate. Therefor transport between compartments is no issue for this compound.
Biodegradation

Value 50% after 5 days and 67% after 20 days.
Breakdown
Product: L(+) lactic acid 80%
Method: BOD (Biochemical Oxygen Demand) and COD (Chemical Oxygen Demand) determinations were carried out for L(+) lactic acid usig the method described in teh Dutch guidenlines "water determination of biochemical oxgen demand after n days (BODn)" (NEN 6634) and "Water determination of chemical oxygen demand (COD" (NEN 6633) respectively, these methods are similar to those referred in the EC Test Guidelines C.8 and C.9 Two concentrations (2 mg/L and 4 mg/L) were tested.
An oculum was prepared from activated sludge. Its microbial activity appeared to be sufficient although the control substance glucose and glutamic acid had a BOD5 of slightly less than the required value of 4.00 ± 0.75 mg O_2/L

References Chapter 2: Environmental fate and pathways

- Lactic Acid: properties and chemistry of lactic acid and derivatives by C.H. Holten,

1971, page 38

- TNO report R 92/018: BOD and COd of L(+) lactic acid according to EC test guidelines C.8 and C.9

- The ecotoxicity and the biodegradability of lactic acid, alkyl esters and lactate salts
  C.T. Bowmer et.al.
  Chemosphere, volume 37, No 7, pp 1317 - 1333, 1998

- Stability of lactic acid and glycolic acid in aqueous systems subjected to acid hydrolysis and thermal decomposition.
  M.M. de Villiers et.al.
  Journal of the society of cosmetic chemists, 48, 165-174 (August 1998)

- Handbook of Chemistry and Physics
  WEAST
  66th Edition

Chapter 3 Ecotoxicity

- ***Acute/Prolonged Toxicity to Fish***

- Type: semistatic
  Species: Brachydanio rerio (Fish, fresh water)
  Exposure period: 48 hour(s)
  Unit: mg/l
  Analytical monitoring: yes
  LC50: = 320 - calculated
  Limit Test: no
  Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
  Year: 1992
  GLP: yes
  Test substance: 80% L(+) Lactic Acid

- Type: semistatic
  Species: Brachydanio rerio (Fish, fresh water)
  Exposure period: 96 hour(s)
  Unit: mg/l
  Analytical monitoring: yes
  NOEC: = 320 - measured/nominal
  LC50: = 320 - calculated
  LC100: = 560 - calculated
  Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
  Year: 1982
  GLP: yes
  Test substance: 88% L(+) Lactic Acid
  Remark: test solutions are not neutralised. It is more than likely that the low pH value affected the survival of the fishes.

- Type: static
  Species: Lepomis macrochirus (Fish, fresh water)
  Exposure period: 96 hour(s)
  Unit: mg/l
  Analytical monitoring: yes
  NOEC: = 56 - measured/nominal
  LC50: = 130 - measured/nominal
  LC50 24h : = 140 - measured/nominal
  LC50 48h : = 130 - measured/nominal
  Limit Test: yes
  Method: :
  The study was conducted at the concentrations of 56; 100, 180; 320 and 560 mg/l. Ten fish with a mean weight of 0.37 g and a mean standard length of 24 mm, were exposed to each test concentration and control.
  The procedures for static bioassay described in (1) and (2) below were used in this experiment.
  (1) Committee on methods for Toxicity Tests with Aquatic Organisms (C.E. Stephan chairman). 1975. Methods for acute toxicity tests with fish, macro invertebrates and

amphibians.
Environmental Protection Agency, Ecological Research Series EPA 660/3-75-009, April 1975; 61p

(2) American Public Health Association. 1980. Standard methods for the examination of water and wastewater. 15th ed. Washington DC 1134p.
Year: 1984
GLP: yes
Test substance: 88% L(+) Lactic Acid
Conclusion:
The results of the four day static fish toxicity studies indicated a 96h LC50 of 103 (100 - 180) mg/l and a No-Observed-Effect Concentration of 56 mg/l. Abnormal effects of mortality and / or surfacing were observed during the 96 hour exposure period. The 24h LC50 was 140 mg/l and the 48h LC50 was 130 mg/l.

- Type: static
  Species: Salmo gairdneri (Fish, estuary, fresh water)
  Exposure period: 96 hour(s)
  Unit: mg/l
  Analytical monitoring: yes
  NOEC: = 56 - measured/nominal
  LC50: = 130 - measured/nominal
  LC50 24h : = 150 - measured/nominal
  LC50 48h : = 130 - measured/nominal
  Method:
  The static fish bioassay was conducted in five gallon glass vessels containing 15 litres reconstituted water. The study was conducted at the nominal concentrations of 32, 56, 100,180 and 320 mg/l. Ten fish were exposed to each test concentration and control.
  Conclusion:
  The results of the four day static fish toxicity studies using test substance are summarised below:
  24-hour LC50 150 mg/l
  48-hour LC50 130 mg/l
  96-hour LC50 130 (100 - 180) mg/l
  96-hour NOEC 56 mg/l

- ***Acute Toxicity to Aquatic Invertebrates***

- Type: static
  Species: Daphnia magna (Crustacea)
  Exposure period: 48 hour(s)
  Unit: mg/l
  Analytical monitoring: yes
  NOEC: = 180 - calculated
  EC50: = 240 - calculated
  EC100: = 320 - calculated
  EC 50 24h : = 240 - calculated
  Limit Test: no
  Method: OECD Guide-line 202
  Year: 1992

GLP: yes
Test substance: 80% L(+) Lactic Acid
Remark:
test solutions are not neutralised. It is more than likely that the low pH values affected the mobility of the daphnia's.

- Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l
Analytical monitoring: yes
NOEC: = 320 - measured/nominal
LC50 48h : = 750 - measured/nominal
Limit Test: yes
Method:

Five concentrations in duplicate of the test compound with ten Daphnia per 250 ml glass beaker were used. The concentrations were a logarithmic series ranging from 100 to 1000 mg/l and included a control. The procedure for static bioassay as described in (1) and (2) below were used.

(1) Methods of acute toxicity with fish, Macro invertebrates and Amphibians. Stephan, CE, chairman. 1975.
Committee on Methods for toxicity tests with aquatic organisms. US EPA Ecol. Res. Ser. 660/3-75009.
(2) American Public Health Association. 1980. Standard methods for the examination of Water and wastewater. 15th ed. Washington DC. 1134p.
Year 1984
GLP: yes
Test substance: 88% L(+) Lactic Acid

- ***Toxicity to Aquatic Plants e.g. Algae***

- Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 70 hour(s)
Unit: g/l
Analytical monitoring: yes
NOEC: = 1.9 - calculated
EC10: = 2.3 - calculated
EC50: = 3.5 - calculated
EC90 : = 5.4 - calculated
Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 1982
GLP: yes
Test substance: 80% L(+) neutralised L(+) lactic acid

- ***Toxicity to Micro-organisms e.g. Bacteria***

- Type: other: laboratory incubations
  Species: Escherichia coli (Bacteria)
  Exposure period: 20 minute(s)
  Unit: g/l
  EC100 : = 15 - measured/nominal
  Test substance`: combinations of 1.0-1.5% lactic acid with 0.1% sodium benzoate, or 0.1% hydrogen peroxide, or 0.005% glycerol monolaurate.
  Result:
  At 22C complete inactivation of E. coli O157:H7 was observed after 20 min. of exposure to 1.5% lactic acid plus 0.1% hydrogen peroxide.
  Conclusion:
  The mentioned treatment could potentially be used to inactivate or reduce E. coli O157:H7 populations on raw products

- Type: other: laboratory incubations on lean beef muscle discs
  Species: other bacteria: Listeria monoccytogenes, Yersinia enterocolitica, Salmonella typhimurium, E.coli, Campylobacter jejuni, Staphylococcus aureus, Pseudomonas fragi, Brochotrix thermosphacta.
  Exposure period: 0 minute(s)
  Remark: Acid temperature (20 & 50 C) and concentration (1%, 3%) and initial numbers of contaminating bacteria (log CFU/cm2 of 3-6) were the variables studied.
  Result: The bactericidal efficacy of lactic acid was often distinct for each organism. Bacterial numbers were maximally reduced with 3% acid at 55C. S.aureus: 1.4 log cycle; P. fragi: 2.3 log cycle; B. thermosphacta: 2.8 log cycle reduction.

References Chapter 3: Ecotoxicity

- Acute / Prolonged toxicity to fish

- TNO report R 91/295; The acute toxicity of L(+)-lactic acid to Brachydanio Rerio (OECD 203).

- Acute toxicity of L(+) lactic acid to Rainbow Trout (Salmo Gairdneri)
  Analytical Biochemistry Laboratories Inc.
  Columbia, MO
  1984

- Acute toxicity of L(+) lactic acid to Bluegill Sunfish (Lepomis macrochirus)
  Analytical Biochemistry Laboratories Inc.
  Columbia, MO
  1984

- Acute toxicity to aquatic invertebrates

- TNO-report R 91/ 294; The acute toxicity of L(+)-lactic acid to Daphnia Magna (OECD 202, 48h).

- Acute toxicity of L(+) lactic acid to Daphnia Magna
  Analytical Biochemistry Laboratories Inc.
  Columbia, MO
  1984

- Toxicity to aquatic plants e.g. algae

- TNO report R 92/009 ; Effect of L(+)-lactic acid on the growth of the alga Selenastrum Capricornutum (OECD 201).

- Toxicity to micro-organisms e.g. bacteria

- Food Microbiology 16: 75-82 (1999), Venkitanarayanan K.S., Zhao T., Doyle M.P., "Inactivation of E.coli 0157:H7 by combinations of GRAS chemicals and temperature".

- Greer G.G. and Dilts B.D., Factors affecting the susceptibility of meat borne pathogens and spoilage bacteria to organic acids.
  Food Research International 25: 355-362 (1992).

Chapter 4 Mammalian toxicity

- ***Toxicokinetics, Metabolism and Distribution***

- In Vitro/in vivo: In vivo
  Type: Metabolism
  Species: mammal
  Remark:

  (L)-lactic acid is a natural functional metabolite in mammal, as mammalian fuel. According to the lactate shuttle concept, L-lactate represents a major means of distributing carbohydrate potential energy for oxidation and gluconeogenesis. The concept of a "lactate shuttle" (Brooks, 1998) is that during hard exercise, as well as other conditions of accelerated glycolysis, glycolic flux in muscle involves L-lactate formation regardless of the state of oxygenation. The production rate of endogenous (L)-lactate in the resting human is about 1.3 mol (70 kg/bw).24 h-1 (= 117 g/day).

- ***Acute oral toxicity***

- LD50
  Species: rat
  Strain: Charles River
  Sex: male/female
  No. of Animals: 55
  Doses: 3,162 / 3,548 / 3,981 / 4,467 / 5,012 / 5,623 / 6,310 mg /kg bw
  LD_{50}: between 3543 and 4936 mg/kg bw
  Method: EPA OPP 81-1
  Year: 1984
  GLP: yes
  Test substance: L(+) lactic acid 80%

- LD100
  Species: rat
  No. of Animals: 10
  Vehicle: water
  Doses: dose was daily increased: 0.25 ml till 4.5 ml lactic acid 50%
  LD_{100}: = 11250 mg/kg bw
  Test substance: L(+) lactic acid 80%
  Remark:
  2 Rats died after dosing with 3 ml = 7500 mg/kg bw. The animals had a 15% reduction in bw in 1 week. A single administration of large doses did not result in changes in carbon dioxide content or pH of the blood, but a considerable decrease in the pH of the urine.

- Single dose toxicity
  Species: rat

Strain:	Charles River
Sex:	male/female
No. of Animals:	10
Doses:	5 mg / kg bodyweight
Method:	EPA OPP 81-1
Year:	1983
GLP:	yes
Test substance:	L(+) lactic acid 80%

Remark:
Test was done to establish clinical signs after single dose treatment
Conclusion:
Four males survived the 14-day duration of the study. One male and all females were found dead on the day of dosing (day 0), on day 1 or on day 10. No abnormal clinical signs were observed during the study.

- ***Acute Inhalation Toxicity***

- Type:	other: Acute inhalation toxicity study
Species:	rat
Strain:	Fischer 344
Sex:	male/female
No. of Animals:	10
Vehicle:	other: aerosol
Doses:	7,94 mg/L (air)
Exposure time:	4 hour(s)
Method:	EPA OPP 81-3
Year:	1987
GLP:	yes
Test substance:	L(+) lactic acid 80%

Conclusion:
Rapid breathing and eye tearing were observed during exposure. One rat from the treated group died on day 9. All other animals survived until the end of the study. Based on these results, the LC50 for L(+)Lactic Acid is greater than 7,94 mg/L.

- ***Acute Dermal Toxicity***

- Type:	LD50
Species:	rabbit
Value:	> 2000 mg/kg bw
Method:	OECD Guide-line 402 "Acute dermal Toxicity"

- Type:	other: Acute dermal toxicity
Species:	rabbit
Strain:	New Zealand white
Sex:	male/female
No. of Animals:	10
Doses:	2 g/kg
Method:	EPA OPP 81-2
Year:	1983
GLP:	yes

Test substance: L(+) lactic acid 80%
Conclusion: All animals survived the 14-days duration of the study and gained body weight. No abnormal clinical signs were observed during the study. Severe erythema and severe oedema were observed at the test sites of all animals after removal on day 1. Erythema decreased in severity for 3 animals on day 12 or 14, and was not observed for one female on day 14.
Oedema decreased in severity for 8 animals and was not observed for one female on day 12 and for one male on day 14. Other dermal reactions observed at test sites included: blanching, necrosis, eschar formation, atonia, desquamation and denuded areas.

- ***Skin Irritation***

- Species: rabbit
  Concentration: 88 %
  Exposure: Occlusive
  Exposure Time: 4 hour(s)
  No. of Animals: 12
  Result: corrosive
  Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
  Year: 1981
  GLP: yes
  Test substance: L(+) lactic acid 88%
  Remark:
  Other studies have shown that the skin of albino rabbit is not the appropriate animal model when addressing the effects of lactic acid on human skin. This result is therefore not used for the classification.

- Species: rabbit
  Concentration: 80 %
  Exposure: Occlusive
  Exposure Time: 4 hour(s)
  No. of Animals: 3
  Result: not irritating
  Method: OECD Guideline 404 "Acute Dermal Irritation/Corrosion"
  Year 1992
  GLP: yes
  Test substance: buffered lactic acid: BF S36 (38% l.a. + 38% sodium lactate, total 76% d.s.). BF S30 (60% l.a. + 20% sodium lactate, total 80% d.s.)
  Remark: When lactic acid is mixed with sodium lactate (buffered to pH 3.0 or 3.6), also in albino rabbits, all skin irritation scores are 0-0.
  Test substance: two types of buffered lactic acid were tested: Purac BF S36 (buffered with Sodium hydroxide to pH 3.6) and Purac BF S30 (buffered with sodium hydroxide to pH 3.0)

- Species: rabbit
  Exposure: Occlusive
  Exposure Time: 24 hour(s)

No. of Animals: 6
Vehicle: other: not applicable
Result: highly irritating
Method: EPA OPP 81-5
Year: 1983
GLP: yes
Test substance: L(+) lactic acid 80%
Conclusion: The observations ranged from: Severe erythema, blanching and yellow-brown colour of the skin, red exudate and skin missing.
No abnormal clinical signs were observed and no mortalities occurred prior to sacrifice after the 30- to 60 minutes.
Under the definition of CFR 49, 173.136, the product does not need to be classified.

- Species: guinea pig
  Concentration: 88 %
  Exposure: Occlusive
  Exposure Time: 4 hour(s)
  Result: not irritating
  Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
  Year: 1981
  GLP: yes
  Test substance: L(+) lactic acid 88%

- Species pig
  Concentration: L(+) lactic acid 88 %
  Exposure: Occlusive
  Exposure Time: 4 hour(s)
  No. of Animals: 3
  |Result: not irritating
  Method: both OECD Guideline 404 (1981) and Directive 84-449 B4
  Year: 1981
  GLP: yes
  Remark: TNO believes the pig to be a more appropriate and representative animal model than the albino rabbit, when addressing the effects of lactic acid on human skin.

- ***Eye Irritation***

- Species: rabbit
  Concentration: 20 % L(+) lactic acid
  Vehicle: water
  Result: irritating
  Method: Journal Officiel de la Republique Francaise procedure; eyes were examined after 1 and 24 h and after 2, 3, 4, and 7 days with fluorescent staining.
  Year: 1973
  GLP: yes
  Result: In same study also 50% sodium lactate was tested,

which is not irritating. Instilled at 20% and 10% provoked significant ocular irritation :Acute Ocular Irritation Index (AOII) was 39.50 resp. 31.17. Only for the 10% dilution these lesions were reversible, 7 days after instillation.

- Species: hen
  Concentration: 88 %
  Dose: 0.03 ml
  Exposure Time: 17 minute(s)
  Comment: rinsed after
  No. of Animals: 4
  Vehicle: none
  Result: highly irritating
  Method: chicken unucleated test
  Year: 1996
  GLP: yes
  Test substance: 88% L(+) Lactic acid aqueous solution

- Species: hen
  Concentration: 73 %
  Dose: 0.03 ml
  Exposure Time: .17 minute(s)
  Comment: rinsed after (see exposure time)
  No. of Animals: 4
  Vehicle: L(+) Lactic acid buffered (pH 3.6) with Sodium Lactate
  Result: highly irritating
  Method: Chicken enucleated eye test
  Year: 1996
  GLP: yes
  Test substance: 73 - 84 % L(+) Lactic acid buffered

- Species: other
  Concentration: 85 %
  Vehicle: other
  Result: irritating
  Only formulation with pH 2.02 (face cream with 11.8% lactic acid 85%) was moderate severe irritant. The formulations with pH ≥ 5.3 were minimal irritant.
  Test condition: in vitro using the Eytex Assay (Avon Products, Inc, 1995). Most of the formulations were tested undiluted. pH of formulations varies from 7.52 to 2.02.

- ***Sensitisation***

- Type: Buehler Test
  Species: guinea pig
  Concentration 1st: Induction 88 % active substance occlusive epicutaneous
  2nd: Induction 25 % active substance occlusive epicutaneous
  3rd: Challenge 88 % active substance occlusive epicutaneous
  No. of Animals: 10
  Vehicle: water
  Result: not sensitising
  Classification: not sensitising

Method: EPA OPP 81-6
Year: 1986
GLP: yes
Test substance: L()+ lactic acid 88%
Conclusion: The reactions seen (very slight to moderate erythema, very slight to moderate oedema) were considered to be irritant reactions, not sensitive reactions. The test article was not considered to be a dermal sensitiser.

- Type: Guinea pig maximisation test
  Species: guinea pig
  Result: not sensitising
  Classification: not sensitising

- ***Repeated Dose Toxicity***

- Type: Sub-chronic
  Species: rat
  Route of administration: gavage
  Exposure period: 90 days
  Frequency of treatment: every day
  Doses: 4 ml lactic acid 10% on 20 g of meal
  Control Group: yes, concurrent no treatment
  Result: No differences in appearance, gross observations at necropsy, or organ weights were observed between the test and control animals. Changes in blood carbon dioxide were slight.

- Type: Sub-chronic
  Species: rat
  Sex: female
  Strain: Sprague-Dawley
  Route of administration: dermal
  Exposure period: 13 weeks
  Frequency of treatment: daily, 5 days/week
  Doses: 886 mg/kg bw
  Control Group: yes, concurrent no treatment
  LOAEL: 886 mg/kg
  Result: No significant gross observations, with the exception of minimal skin irritation. Absolute brain weight and kidney-to-body weight ratios were increased for test animals. No lesions were observed at necropsy or at microscopic examination.
  Conclusion: formulation (face cream containing 0.25% of lactic acid 85%) is safe in terms of cumulative toxicity. Based upon the exaggerated dose level used in this study for skin care products, dermal application is not likely to produce adverse effects under conditions of consumer use.

- Type: Sub-chronic
  Species: rat
  Sex: male/female
  Strain: Fischer 344
  Route of administration: experiment I: calcium lactate dissolved in drinking water

(up to 5%).

experiment II: up to 30% calcium lactate in diet.

Exposure period: 13 weeks
Frequency of treatment: daily
Test substance: Calcium lactate as a salt of lactic acid.
Doses: 5, 2.5, 1.25, 0.6, 0.3 %
Control Group: yes, concurrent no treatment
Remark: Lactic acid tested as its Calcium salt. From this study the lactate part is relevant, should be separated from effects of the soluble Calcium intake.
Result: a <10 % decrease in body weight gain. all animals survived. some haematological and biochemical parameters changed, but no severe lesions were found in microscopic examination in the experiment with ca-lactate mixed in the diet, the amount of calcium in the urine was significantly increased. Nephrocalcinosis and degeneration in kidneys observed. Indications that Nephrocalcinosis was dependent on the low Ca/Phosphorus ratio of the synthetic diet.

- Type: Sub-chronic
  Species: Syrian hamster
  Sex: male/female
  Route of administration: other: Group 1 (control):Diet 1, contains 20% sucrose as carcinogenic diet; pure water to drink. Group 2: diet 1, mixed with 0.057 ml lactic acid 80%; pure water to drink. Group 3: same diet 1, but water containing 0.050% v/v lactic acid
  Exposure period: 14 weeks
  Frequency of treatment: daily ad libitum; animals of groups 2 & 3 ingest same amount lactic acid.
  Post exposure period: sacrificed and autopsy; also oral cavity (caries incidence)
  Control Group: yes, concurrent no treatment
  Remark: pH of diet 1 is 5.55, of diet 2 is 5.12. pH of pure water is 6.8 and of water + lactic acid is 3.1 .
  Result: three groups same growth and health. No significant differences were found in the incidence or extent of carious lesions among the three groups.
  Conclusion: dietary lactic acid did not play any important role in development or progress of dental caries.

- ***Genetic Toxicity 'in Vitro'***

- Type: Ames test
  System of testing: S. typhimurium strains TA97, TA98, TA100, TA104
  Concentration: 0.5, 1.0, and 2.0 microliter lactic acid/plate
  Metabolic activation: with and without
  Result: negative
  Type: Salmonella/microsome test (Ames test) and chromosomal aberration test in vitro
  System of testing: reverse mutation assays, and Chinese hamster fibroblast cell line
  Concentration: 10 mg/plate, resp. 1.0 mg/ml
  Metabolic activation: without

Result: negative

- Type: Chinese hamster ovary K1 cells, chromosomal aberration tests, and the pH relationship of the medium and clastogenic activity was examined.
  System of testing: Cells were maintained in Ham's F12 medium, supplemented with 10% foetal calf serum.
  Concentration: 8-35 mM
  Cytotoxic Concentration: 14-35 mM, when pH was <= 5.8
  Metabolic activation: with and without
  Result:
  When the culture medium was first acidified by the lactic acid dose and then neutralised to pH 6.4 or when medium is containing 30 mM HEPES as buffer, lactic acid was non-clastogenic.
  Pseudo-positive reactions are seen as a result of non-physiological low pH.

- Type: review on several mutagenicity studies with lactic acid and some lactates.
  System of testing: various
  Concentration: various
  Metabolic activation: with and without
  Result: negative
  Result: the result of 11 studies is reviewed.

- ***Genetic Toxicity 'in Vivo'***

Due to the natural nature of L(+) lactic acid and the relative low contribution of "outside L(+) lactic acid" to the human metabolism, in vivo genotoxicity studies will not be required.

- ***Carcinogenicity***

- Species: rat
  Sex: male/female
  Strain: Fischer 344
  Administration: drinking water
  Exposure period: 2 years
  Frequency of treatment: daily, ad lib.
  Post exposure period: Autopsy on rats that died during study and those killed at the end. Examination macro-and microscopically for presence of non-neoplastic and neoplastic lesions
  Doses: 2.5 or 5 % Calcium lactate in the drinking water. Mean total Calcium lactate intake for males was 329.4 g, resp. 625.4 g; for females 237.7 g, resp. 412.1 g.
  Result: negative
  Control Group: yes, concurrent no treatment
  GLP: yes
  Test substance: The Calcium salt of lactic acid was tested
  Remark: Lactic acid tested as its Calcium salt. From this study the lactate intake is relevant, should be separated from the Calcium effects of a soluble Calcium salt.

- Species: rabbit
  Sex: female
  Administration: drinking water
  Exposure period: 5 or 13 months
  Frequency of treatment: twice daily
  Doses: 0.1-0.2 g/kg bw (5 months), and 0.1-0.7 g/kg bw (13 months)
  Result: negative
  Control Group: no data specified
  Result: No tumors were reported after 5 or 16 months. Further details not provided.

- ***Toxicity to Fertility***

The nature of the compound (part of human metabolism) does make toxicity studies to fertility not necessary

- ***Developmental Toxicity/Teratogenicity***

- Species: mouse
  Sex: female
  Strain: CD-1
  Administration: gavage
  Exposure period: gestational days 6-15
  Frequency of treatment: daily
  Duration of test: 10 days
  Doses: 570 mg/kg bw/day
  Control Group: yes, concurrent no treatment
  NOAEL Maternal Toxicity: >= 570 mg/kg bw
  NOAEL Teratogenicity: >= 570 ml/kg bw
  Result: Lactic acid was neither maternotoxic nor embryofetotoxic when given orally to mice at 570 mg/kg bw/day on gestation days 6-15.

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