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Safety Assessment of Polylactide (PLA) for Use as a Food-contact Polymer

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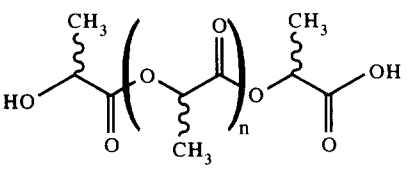
Abstract—This report constitutes a safety assessment of polylactide (PLA), a polymer of lactic acid intended for use in fabricating various food-contact articles. Migration studies were conducted on samples of the polymer following guidelines issued by the Food and Drug Administration. Potential migrants from PLA include lactic acid, lactide (the monomer), and lactoyllactic acid (the linear dimer of lactic acid). The studies were designed to model reasonable 'worst' case extraction situations when the polymer is used (a) in houseware articles for short and intermediate time periods at various temperatures and (b) in food-packaging materials. The limited migration observed during the trials represents no significant risk since migrating species are expected to convert to lactic acid, a safe food substance. It is concluded that PLA is safe and 'Generally Recognized As Safe' for its intended uses as a polymer for fabricating articles that will hold and/or package food.

INTRODUCTION

Polylactide (PLA) is a polymer resulting from the polymerization of lactic acid by the ring opening of its cyclic dimer, lactide. The repeat unit in the polymer chain is lactic acid. The chemical structure of PLA is depicted in Fig. 1 and that of lactide in Fig. 2. Because it can be hydrolysed, the polymer has been previously studied for use in bioabsorbable medical devices, for example in suturing material (In de Braekt *et al.*, 1992), surgical implants (Bos *et al.*, 1991; Laitinen *et al.*, 1992; Matsusue *et al.*, 1992) and drug-delivery systems (Bodmeier *et al.*, 1989; Conti *et al.*, 1992; Omelczuh and McGinity, 1992; Suzuki and Price, 1985). The objective of our safety assessment was to determine whether PLA is 'Generally Recognized As Safe' (GRAS) when used in fabricated articles to hold or package food. In accordance with Food and Drug Administration (FDA) regulations, this determination was based on 'those human, animal, analytical and other scientific studies, whether published or unpublished, appropriate to establish the safety of the substance' [21 C.F.R. §§ 170.30(b) and 170.3(h)].

The uses of PLA considered as part of this safety assessment involve applications such as disposable cutlery, cups, plates, straws, stirrers, lids, certain packaging applications, and cups, plates and containers for foods dispensed at delicatessens and fast-food establishments. These articles will be in contact with aqueous, acidic and fatty foods that are (a) dispensed and maintained at or below room temperature, or (b) dispensed at temperatures as high as 60°C, and then allowed to cool to room temperature or below. Uses at temperatures higher than 60°C [the glass transition temperature (T_g) of PLA] were not investigated as part of this assessment.

The safety of food-contact polymers is evaluated by considering the identity, toxicological properties and quantities of substances that migrate from the



PLA

Fig. 1. Chemical structure of polylactide (PLA).

Abbreviations: CF = consumption factor; EDI = estimated daily intake; FDA = Food and Drug Administration; GC = gas chromatography; GRAS = generally recognized as safe; JECFA = Joint FAO/WHO Expert Committee on Food Additives; LC = liquid chromatography; PLA = polylactide; RLM = residual lactide monomer; SCOGS = Select Committee on GRAS Substances; T_g = glass transition temperature; THF = tetrahydrofuran.

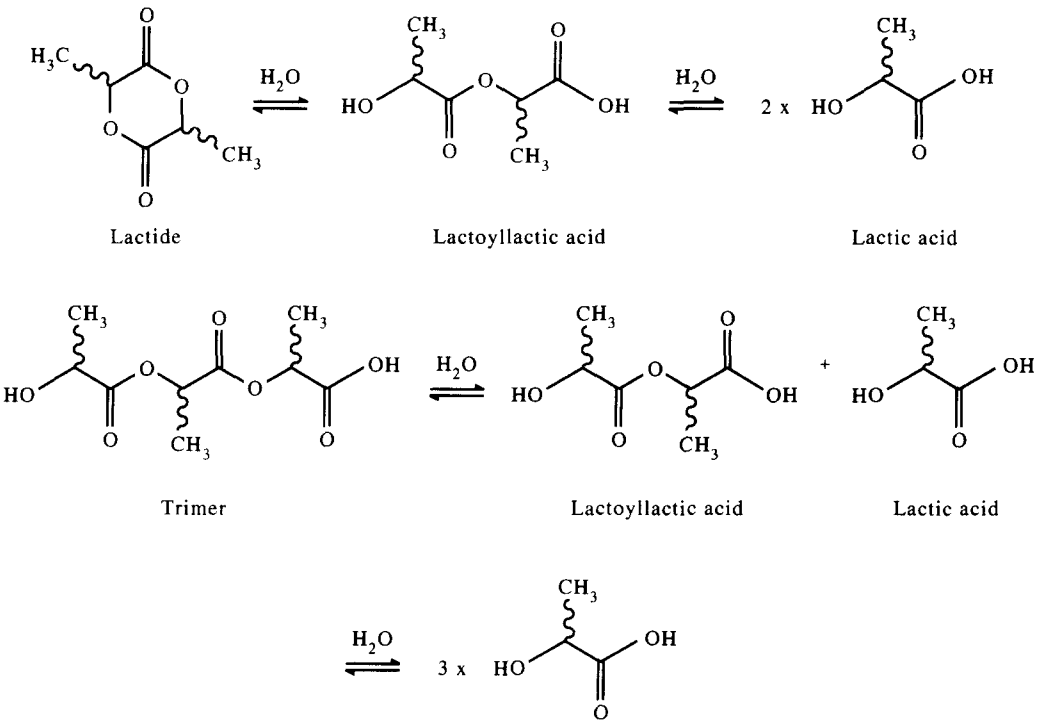


Fig. 2. Chemical equilibria illustrating relationship between lactic acid, its linear dimer (lactoyllactic acid) and trimer, and lactide.

polymers into food during conditions of intended use. Migrants from PLA may include lactic acid, lactoyllactic acid (the linear dimer of lactic acid), other small oligomers of PLA (trimer etc.), and lactide (the cyclic dimer of lactic acid and the monomer used to build the polymer). Lactic acid is the substance of primary interest, since the other species are expected ultimately to hydrolyse to lactic acid either in the aqueous or the acidic media commonly found in food systems or in the human digestive tract. Because information on the hydrolysis behaviour of the monomer lactide was limited, studies were conducted to confirm that it readily hydrolysed under conditions relevant to the uses of PLA.

Migration of PLA components was determined in extraction tests in which samples of the polymer were exposed to food-simulating solvents under conditions that reproduced the most severe temperature/time conditions to which food would be exposed while in contact with PLA. These simulated conditions included contact with aqueous, acidic and fatty foods under the following four conditions: (1) short-term use at room temperature or below where PLA contacts foods for less than 0.5 hr; (2) uses of intermediate duration where PLA is in contact with food at room temperature for a period of 0.5 hr to 1 day; (3) houseware applications, where food is dispensed at elevated temperatures (maximum temperature 60°C) and then cooled to room temperature; and (4) more extended periods of contact at room temperature or below. Category 1 is expected to represent most uses of PLA, including applications with food serviceware and other single-use disposable articles. The second category simulates those limited circumstances where PLA articles will be used repeatedly as houseware articles and in applications where foods are dispensed at delicatessens and fast-food establishments and then taken home and stored before consumption. The third category includes special applications such as plates for hot foods. The final category encompasses those limited applications where PLA would be used as a food-packaging material. All extraction tests were designed to follow FDA guidelines for extraction studies on materials

Table 1. Characterization of PLA films used in migration studies

Film	RLM (%)	M_n	M_w	Thickness (mil)	T_g (°C)	Meso-lactide content (%)
1	0.3	79,000	180,000	24 ± 2	60.5	12
2	0.5	75,000	176,000	23 ± 1	59.5	12
3	0.8	75,000	175,000	25 ± 2	59.5	12
4	1.8	73,000	221,000	24 ± 2	57.6	11
5	2.5	42,400	112,000	24	56.4	17

RLM = residual lactide monomer M_n = number average molecular weight M_w = weight average molecular weight T_g = glass transition temperature

Table 2. Short- and intermediate-term aqueous trials: total lactic acid migration at 0.5–24 hr

Time (hr)	Lactic acid migration (μg/sq. in.) 26°C (1.8% RLM)	43°C (0.8% RLM)	43°C (1.8% RLM)
0.5	2.5	8.6	10.7
1	3.2	9.2	11.4
2	3.4	10.4	13.5
4	3.4	11.8	14.4
8	4.8	16.2	20.4
12	4.4	—	23.6
16	5.1	17.3	—
20	4.9	18.1	26.4
24	6.1	18.6	29.2

RLM = residual lactide monomer

contacting food (FDA, 1993), with certain adaptations made, where appropriate and as described below, to reflect the special physical characteristics of PLA.

MATERIALS AND METHODS

Migration studies

PLA sheet. PLA films for extraction testing were prepared according to Gruber (Gruber *et al.*, 1992). Sheet (20–25 mil) was extruded on Killion equipment, 30/1 L/D with a 6-in. (≈152 mm) sheet die. Extrusion conditions were as follows: zone 1, 300°F; zone 2, 320°F; zone 3, 365°F; adapter, 365°F; die, 365°F; melt temperature, 345°F; screw speed, 25 rpm; melt pressure, 200 psi (≈1380 kPa). The residence time, determined using tracer pellets, was 1.5 min. Properties of the prepared PLA films are described in Table 1.

Extraction studies. PLA sheet (20–25 mil thick) was cut into rectangular pieces measuring 1 in. by 0.625 in. (≈25.4 × 16 mm) using a paper-cutter. For the long-term studies and studies conducted at elevated temperatures, three strips were placed in a 20-ml scintillation vial using a spiral steel clip to separate the strips and to expose the surface area of each strip [3.75 sq. in. (≈24.2 sq. cm) of surface area]. For all other studies, six strips of PLA [7.5 sq. in. (≈48.4 sq. cm) of surface area] were used. 10 ml solvent (8% ethanol, 3% acetic acid, or food oil) was added to each vial. The vials were placed in an orbital shaker at 26 or 43°C. Extract samples were removed from the shaker at appropriate times. The PLA pieces were removed from the extraction vial and placed in a clean 20-ml scintillation vial. Extract samples were immediately prepared for liquid chromatography (LC) or frozen (−15°C) until prepared.

Table 4. Comparison of data for hot food dispensing with cooling to a constant temperature, trials at 26°C and 43°C*

Conditions	Migration (μg/sq. in.)
26°C, 1 day	9.6 ± 1.2
43°C, 1 day	27.7 ± 1.2
60°C → rt, 1 day	24.3 ± 2.2

rt = room temperature

*All trials used 0.8% residual lactide monomer film. Values are means of triplicate determinations ±SD.

Elevated temperature extraction trials. The solvent (10 ml 8% ethanol) was heated in the scintillation vial to 60°C. The extraction cell was removed from the water-bath and three rectangular pieces of PLA (3.75 sq. in.) were added as above. The extraction vial was allowed to cool to room temperature under ambient conditions (40 min to 26°C) and aged to 24 hr. Extract samples were removed from the vials and treated as described.

Hydrolysis of lactide. A 100 or 1000 ppm solution of L-lactide was prepared by diluting a 1% solution of lactide in acetonitrile with distilled water or 8% ethanol at the appropriate temperature. Samples were aged at the respective temperatures, removed at various times and analysed directly by gas chromatography (GC).

Lactide hydrolysis in 0.1 N HCl. Solutions of approximately 1250 ppm L-lactide in 0.1 N HCl at 37°C were prepared by adding 100 μl L-lactide solution (0.25 g/ml) in tetrahydrofuran (THF) to 20 ml of 0.1 N HCl, heated to 37°C, in 25-ml volumetric flasks. The flasks were stoppered and aged at 37°C. Flasks were removed at various times, immediately cooled to room temperature in a cold water-bath, diluted to volume (1000 ppm theoretical), mixed thoroughly, and analysed directly by GC.

Preparation of samples for LC

From extraction in 8% ethanol. 1.5 ml 8% ethanol extraction solution was added to a 2.0-ml volumetric flask. The solution was saponified by the addition of 0.1 ml 0.25 N sodium hydroxide followed by heating for 15 min in a water-bath at 60°C. After cooling, the solution was acidified with 0.15 ml 0.25 N sulfuric acid and diluted to volume with 8% ethanol.

Table 3. Long-term aqueous trials: total lactic acid migration at 1–15 days

Time (days)	Temp. (°C)	Lactic acid migration (μg/sq. in.) 0.3% RLM	0.5% RLM	0.8% RLM	1.8% RLM
1	26	5.9 (0.9)*	—	9.7 (1.2)	9.2 (1.3)
5	26	8.1 (0.4)	—	8.5 (2.1)	10.0 (0.4)
10	26	5.2 (0.4)	—	11.1 (1.1)	9.8 (2.0)
15	26	5.5 (0.6)	—	9.8 (1.0)	11.2 (0.3)
1	43	15.8 (0.4)	18.0 (0.7)	27.7 (1.2)	—
5	43	23.0 (1.0)	26.3 (1.6)	47.8 (4.2)	—
10	43	24.5 (1.3)	31.1 (1.2)	55.1 (1.3)	—
15	43	28.9 (1.8)	35.5 (2.7)	—	—

Values are means of triplicate determinations; ±SD in parentheses.

Table 5. Comparison of migration into acidic and aqueous food-simulating solvents at 43 C

Film*	Solvent	Migration (μg/sq. in.)
1	Acetic acid (3%)	< 16.6
1	Ethanol (8%)	13.1
3	Acetic acid (3%)	18.6
3	Ethanol (8%)	25.2

*See Table 1 for description of films.

From extraction with 3% acetic acid. 1.0 ml 3% acetic acid extraction solution was added to a 2.0-ml volumetric flask. The solution was saponified by the addition of 0.5 ml of 2.0 N sodium hydroxide followed by heating for 15 min in a water-bath at 60°C. After cooling, the solution was acidified with 0.3 ml 4.0 N sulfuric acid and diluted to volume with 3% acetic acid.

From extraction with Miglyol (fractionated C_8–C_{10} coconut oil triglycerides from Huls America, Inc., Piscataway, NJ, USA). Water (10 ml) was added to the oil at the end of the extraction period. The samples were agitated on an orbital shaker for 16 hr. Good contact of the phases was important but too vigorous agitation led to emulsions that were difficult to break. The aqueous phase was saponified in the same manner as the samples extracted with 8% ethanol.

LC parameters. Shodex Ionpack column; 0.1% phosphoric acid mobile phase; 60°C; 1 ml/min; UV detector, 209 nm. Lactic acid eluted at approximately 9 min. The system was calibrated with standards prepared from crystalline lactic acid.

GC parameters. HP 5890, DB-17 capillary column (J & W), 30 m × 0.25 mm, 0.25 μm film thickness. Injector (split, 100:1), 200°C; detector, 260°C. Temperature programme: 10 min at 100°C, 10°C/min to 250°C, 3 min at 250°. Retention times: meso-lactide, 13.4 min; L-lactide, 14.6 min.

Validation

8% ethanol. The method was validated by spiking lactide into 8% ethanol, saponifying, and measuring recovery by LC. Samples from the longest extraction times of many experiments were also validated by spiking at ×0.5, ×1 and/or ×2 the lactic acid found in the extract solutions. Several extract samples were combined to create a large enough volume of homogeneous solution for spiking. Lactic acid was spiked directly into the solution which was then prepared for LC by saponification.

Table 6. Comparison of migration into fatty and aqueous food-simulating solvents at 43 C*

Time (days)	Lactic acid migration (μg/sq. in.)	
	Miglyol	8% Ethanol
1	23.1 (3.0)	119 (2.2)
2	25.9 (2.3)	145 (10.5)
3	24.2 (5.0)	152 (19.4)
5	25.7 (2.2)	—
10	27.9 (0.8)	—

*Trials conducted with PLA film 5 (see Table 1). Values are means of triplicate determinations for miglyol and duplicate determinations for 8% ethanol (±SD in parentheses).

3% acetic acid. Validation was performed in the same manner as for 8% ethanol extractions.

Miglyol extractions. The method was validated by spiking lactide into Miglyol, partitioning into water, saponifying, and measuring the recovery of lactic acid by LC. Samples were spiked by addition of lactide to the Miglyol at the end of the extraction time and partitioning into water followed by saponification.

RESULTS

Migration experiments

Aqueous food trials. Table 2 includes migration data from 0.5 to 24 hr for PLA films at 26 and 43°C. The 26°C data reflect the expected migration during single-use, disposable applications of PLA involving short-term (0–0.5 hr) and intermediate-term (0.5–24 hr) periods of food contact. The temperature (26°C) is slightly higher than the 20°C recommended by the FDA for providing 'worst case' projections for short-term uses because 26°C was experimentally easier to hold constant. Table 2 also includes short-term migration data at 43°C, which were used to develop a diffusion model, discussed below.

Table 3 contains 1–15-day data at 26 and 43°C for samples of PLA containing varying residual lactide monomer (RLM) levels. The 26°C data represent accelerated shelf-life for refrigerated and frozen-food packaging applications. The 43°C data model accelerated shelf-life studies for room temperature applications. The temperature (43°C) is lower than the 49°C recommended by FDA; the lower temperature

Table 7. Diffusion coefficients of lactide from PLA film into 8% ethanol*

Film RLM content (%, w/w)	Temp. (°C)	Duration (hr)	Intercept (μg/in²)	Diffusion coefficient (cm²/sec)
1.8	26	24	1.8	3.8×10^{-15}
0.3	26	360	5.7	n.m.
0.8	26	360	7.2	n.m.
1.8	26	360	6.7	1.4×10^{-16}
0.8	43	24	5.7	2.6×10^{-13}
1.8	43	24	5.6	1.6×10^{-13}
0.3	43	360	9.6	2.2×10^{-13}
0.5	43	360	9.6	1.5×10^{-13}
0.8	43	240	12.8	2.8×10^{-13}

n.m. = not measurable

*Data taken from short-term (0.5–24 hr) and long-term (1–15 days) experiments at 26 and 43 C.

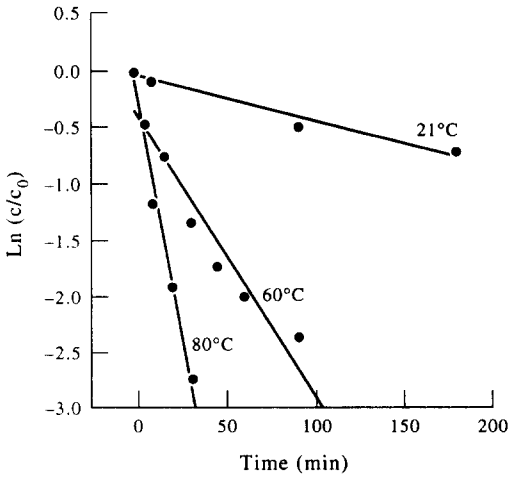


Fig. 3. Lactide hydrolysis data in 8% ethanol at 21°C and in water at 60 and 80°C.

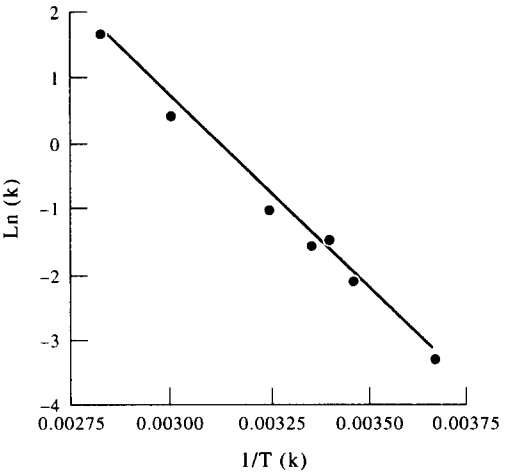


Fig. 4. Arrhenius plot: experimental and literature rate constants (k, hr^{-1}) for lactide hydrolysis in water and 8% ethanol, 0–80°C.

was used because 49°C approached the T_g of PLA. To compensate for using a lower temperature, the experiments were carried out for 15 days instead of the 10 days recommended by FDA.

In a final aqueous trial, PLA samples were immersed in 8% ethanol at 60°C and then allowed to cool to room temperature. Extracts were tested after 1 day of exposure. These trials reflect expected migration behaviour when hot food is dispensed into a PLA article and consumed while cooling. Table 4 compares the results of this trial with 1-day data from two trials where the temperature was held steady (26 and 43°C).

Acidic food trials. Two migration experiments were performed using 3% acetic acid as an acidic food-simulating solvent: one was a screening experiment where films were compared at two different lactide levels for film hazing and migration; the second was a 15-day migration study. In the screening experiment, a 0.8% RLM film and a 1.8% RLM film were incubated in 8% ethanol and 3% acetic acid at 43°C. The samples were observed twice a day. Haze formation was observed in the two 0.8% films at the same time (102 hr) and in the two 1.8% films at the same time (69 hr). These observations indicate that, when these aqueous and acidic systems are compared, physical changes in the PLA films are a function of residual monomer content, but not a function of the solvent. More quantitative information regarding the behaviour of PLA with acidic foods was gathered in a trial where 0.3% RLM and 0.8% RLM films were extracted in ethanol and acetic acid for 24 hr at 43°C. The extraction data are tabulated in Table 5 and show that there was no more migration into the acidic medium than into a neutral one. This result was confirmed in a 15-day trial using 0.3% RLM film where all extraction results into 3% acetic acid were below the detection limit of 16.6 μg/sq. in (≈2.6 μg/sq. cm) for this system. In the corresponding extraction in 8% ethanol, where the detection limit was 3.6 μg/sq. in (≈0.56 μg/sq. cm), results ranged from 13 to 25 μg/sq. in (≈2.0–3.9 μg/sq. cm).

Fatty food trials. Preliminary results indicated that migration into fatty food simulating solvents was much less than that observed in the other systems. Therefore, a PLA film with low molecular weight and high RLM content was used at 43°C to measure migration into oil, since this combination was expected to result in exaggerated migration levels that

Table 8. Hydrolysis rate for L-lactide in aqueous media

Temp. (°C)	k* (per hr)	Half-life (hr)	Source
80	5.39	0.13	Aqueous
60	1.54	0.45	Aqueous
35	0.36	1.9	Aqueous*
25	0.21	3.3	Aqueous*
21	0.23	3.0	8% ethanol
16	0.12	5.8	Aqueous*
0	0.036	19.8	Aqueous*
35	2.17	0.3	0.1 N HCl*
37	1.68	0.4	0.1 N HCl

k = rate constant

*From Holten (1971).

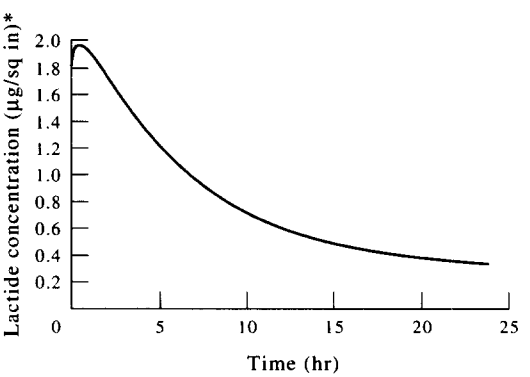


Fig. 5. Lactide concentration: model of 1.8% RLM film at 26°C. *Values have been converted from 'total lactic acid', as determined in migration studies, to lactide by correcting for addition of two water molecules during hydrolysis of lactide.

Table 9. Lactic acid content of some foods and its calculated annual per capita consumption in the United States

Food	Lactic acid content (g/kg)	Per capita consumption of commodity (kg/yr)*	Per capita lactic acid annual consumption (g)
Pork	9	30.4	274
Beef	9	46.7	420
Edible offal	9	3.9	35
Cheese (natural)	13	10.1	140
Buttermilk	10	1.0	9.5
Poultry	10	36.7	367
Yogurt	10	2.1	21
Sauerkraut	11	0.2	2.4
Veal	9	0.8	6.9
Mutton	9	0.8	6.9

*USDA/ERS (1991); 1988 consumption values are used.

would exceed the detection limit. The data are reported in Table 6 and compared with aqueous data under the same conditions. The overall level of migration into the fatty food simulating solvent was approximately one-sixth that observed in the aqueous system.

Diffusion model. The observed migration behaviour is characterized by an initial, elevated rate of migration followed by a slower rate. The slower rate results in an increase in the level of migrants that is proportional to the square root of time. This relationship is consistent with the expected diffusion mechanism. Data from both short-term and long-term studies were analysed in the context of a diffusion model using results from aqueous trials. A semi-infinite slab model was used and the concentration of lactide at the surface was taken to be zero because the lactide concentration in the bulk was not significantly changed during these studies and the lactide concentration in solution was very small.

The data for each experiment were analysed independently to determine the intercept (i.e. the initial, rapid build-up) and the diffusion coefficient. The diffusion coefficient, D, is related to the slope of a plot of lactide concentration *v.* the square root of time by the formula $D = \text{slope}^2\pi/(2\rho C)^2$, where ρ = density and C = the concentration of lactide in the PLA film (Sherwood *et al.*, 1975).

Results are listed in Table 7. Good agreement was obtained for all experiments at a given temperature, with a diffusion coefficient of approximately 2×10^{-13} cm^2/sec for lactide in PLA at 43°C, and approximately 4×10^{-15} cm^2/sec at 26°C. This 50-fold difference in the diffusion coefficient over a 17°C temperature range corresponds to an activation energy of 43 kcal/mol. This is a high value for typical diffusion processes, but is consistent with diffusion of a large molecule in a polymer below T_g (Crank and Park, 1968).

Hydrolysis experiments

The analytical procedures for determining the migration of mobile components from PLA converted all species to lactic acid and determined them as such. The chemical relationship between the various potential migrants is illustrated by the chemical equilibria depicted in Fig. 2. In the presence of significant quantities of water, both forward reactions are essentially irreversible. Experiments were performed to determine the rate at which lactide would hydrolyse in an aqueous food system (i.e. 8% ethanol, room temperature) and in the stomach (0.1 N HCl, 37°C). Additional aqueous trials were carried out at 60 and 80°C. The aqueous data are presented graphically in Fig. 3. The linear plot on a semi-log graph is consistent with the expected first-order kinetics. The slopes of these plots give the hydrolysis rate constants reported in Table 8. Values for aqueous hydrolysis obtained from graphs in Holten (Holten, 1971) are also included in Table 8 and are in good agreement with experimental values. These data are plotted in Arrhenius form in Fig. 4, showing an activation energy of 11.6 kcal/mol for lactide hydrolysis over this temperature range. The presence of ethanol did not appear to have a major effect on the rate of hydrolysis. The data for HCl are not included in the activation energy calculation; as expected, they showed a higher hydrolysis rate.

Given the rate of hydrolysis, the concentration of lactide in aqueous and acidic foods will be significantly reduced as a result of hydrolysis. As listed in Table 8, lactide has a half-life of 3.0 hr in an aqueous medium at room temperature. In addition, any lactide remaining unhydrolysed at the time of ingestion will be subject to rapid hydrolysis in the stomach. Lactide has a half-life of 0.4 hr in a 0.1 N HCl solution at 37°C. The concentration of lactide in solution, assuming that lactide initially comprises all of the migrating species, was modelled based on the diffusion coefficients and the hydrolysis rates described above. Figure 5 shows the results from the 1.8% RLM film at 26°C. The graph shows the interplay of two competing rates—the rate of diffusion into food

Table 10. Estimated lactic acid intake by infants 8–195 days of age

Volume intake (ml/kg body weight)	Lactic acid concentration (mg/dl)	Daily lactic acid intake (mg/kg)
140 (10th percentile)	6	8
150 (50th percentile)	6	9
165 (90th percentile)	6	10

Table 11. Migration data used to calculate EDI

	Migration data (μg/sq. in.)			
	Aqueous and acidic foods		Fatty foods	
PLA application	Value	Source	Value	Source
Short-term housewares (0–0.5 hr food contact)	1.3*	Table 2, 26°C, 0.5 hr	0.22	**
Intermediate-term housewares (0.5–24 hr)	7.6†	Tables 2 and 3, 26°C, 24 hr	1.3	**
Hot food dispensing	24.3	Table 4, 60°C→rt, 1 day	4.0	**
Long-term (packaging)	11.2	Table 3, 26°C, 15 days, 1.8% RLM‡	9.2	§

*Value represents half of the migration reported for the short-term tests. The total level of migration was divided by a factor of 2 to account for the disappearance of food over the course of the 0.5 hr contact (i.e. the quantity of food available to receive migrating species will continually decrease over the course of 0.5 hr interval). In arriving at this figure it was assumed that the food disappears at a steady rate and is completely consumed after the 0.5 hr period.

**Represents one-sixth corresponding value from aqueous trials.

†Value represents average of data points appearing in Tables 2 and 3 for different trials.

‡Datum selected from 26°C trial, which simulated extended shelf-life for frozen and refrigerated foods. Data for 43°C trial not relevant because technical limitations preclude prolonged contact between polymer and water.

§Represents one-sixth value for aqueous trial at 43°C, 10 days, 0.8% RLM. Using 43°C data (representing extended shelf-life at room temperature) is appropriate for fatty foods because hydrolysis of polymer will not occur during prolonged contact with fatty foods.

as modified by the rate of hydrolysis. The maximum of the plot occurs at 0.4 hr and the lactide concentration drops quickly thereafter.

DISCUSSION

Lactic acid is the ultimate product of hydrolysis of any chemical species that might initially migrate from PLA into foods contacting the polymer. Thus, lactic acid is the primary focus of concern in evaluating the safety of PLA as an indirect food additive.

Lactic acid has a long history of use in food and is considered safe when used both as an intentional food ingredient and when naturally occurring in food. The substance (L-isomer, D-isomer, DL mixture) was affirmed as GRAS in 1984 by the FDA for individuals beyond infancy. The current regulation, at 21 C.F.R. § 184.1061, approves the use of the substance in the general food supply without limitations, except for those imposed by good manufacturing practice. Among the applications of lactic acid affirmed as GRAS are use as a curing and pickling agent, a flavour enhancer, a flavouring agent, an adjuvant, a pH control agent, and a solvent and vehicle. The only restriction in the regulation is that lactic acid should not be added as an acidifying agent to infant formula products. This restriction was based on the possibility that the limited ability of infants to metabolize the D-isomer of lactic acid might lead to an organic acidosis in these subjects [Select Committee on GRAS Substances (SCOGS), 1978].

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) set no limits on the addition of lactic acid to foods for the general population (JECFA, 1965, 1973 and 1974), but it did recommend that neither the D(−)-lactic acid or DL-lactic acid be added to formulas for infants less than 3 months of age. The European Community's Scientific Committee on Food reached the same conclusion (Commission of the European Communities, 1991). The Japanese Standards of Food Additives (Japanese Union of Food Additive Associations, 1974) set a maximum of 10,000 ppm calcium in the form of added calcium lactate, but set no limits for lactic acid.

Exposure data

Current levels of dietary intake of lactic acid can be considered from several perspectives. As shown below, these levels greatly exceed any contribution from the intake of lactic acid as a result of foods contacting PLA. FDA-sponsored poundage surveys conducted by the National Academy of Sciences in 1975, 1982 and 1987 indicate that the per capita intake of lactic acid added to foods amounts to about 22 mg/day (National Research Council, 1989) (corrected for an expected 60% response rate from the survey). This value is reasonably close to the intake of 15 mg lactic acid estimate for lactic acid intake made in 1978 by the Select Committee for GRAS Substances.

Much higher figures of daily intake of added lactic acid were calculated from data provided by the US Department of Agriculture, based on estimates of portion size, Market Research Corporation of America data on frequency of eating foods in several categories, and the assumption that all foods within each food category contain the substance at the high levels reported for some representative samples. These data led to the conclusion that the average daily intake of lactic acid from all sources was 924 mg/day for those 2 yr of age and older, and 377 mg/day for calcium lactate for the same group. However, as pointed out by the National Academy of Sciences Subcommittee, and as explained in Section XI of the National Research Council's Subcommittee on Review of the GRAS List, this method of

estimation is likely to lead to overstated estimates of intake, often by considerable margins (Subcommittee on Review of the GRAS List, 1972).

A final perspective on lactic acid intake is provided by considering its natural occurrence in foods. Table 9 includes a partial list of foods where lactic acid is naturally present, and reports its concentration in those foods. These data suggest that the dietary intake of indigenous lactic acid could be as much as several grams per day.

Finally, infants consume lactic acid from breast milk. L(+)-Lactic acid occurs in human milk at a concentration of 60 mg/litre (Wallace *et al.*, 1992). Using published volume intake data (Fomon, 1993) and assuming that human milk and infant formula have equivalent energy density, it is possible to estimate the daily intake of L(+)-lactic acid by the breast-fed infant. These data are summarized in Table 10; a breast-fed infant weighing 4 kg would consume about 36 mg L(+)-lactic acid/day.

In contrast to these values, our review of the migration data for PLA leads to the conclusion that the amount of PLA (and its equivalent amount of lactic acid) entering food through its migration from different types of food packaging materials and from food containers or utensils would be very small. The amount entering food can be computed according to the following equation: $CF \times 0.1 \times [(F_{aq}) \times$ (migration into aqueous and acidic foods observed in short-term, intermediate-term, long-term, and hot food dispensing trials) + $(F_{fat}) \times$ (total migration into fatty foods observed in short-term, intermediate-term, long-term, and hot food dispensing trials)].

CF is the consumption factor for PLA, which represents the percentage of the diet expected to contact articles fabricated from PLA. A value of 5% was used for this value, which corresponds to the minimum CF permitted by the FDA (FDA, 1993). The factor of 0.1 is used to convert the migration data (in μg/sq. in) to a dietary concentration (in parts per million, ppm). Consistent with FDA guidelines, the factor assumes that 10 g food are in contact with each square inch of packaging surface. F_{aq} and F_{fat} represent the relative proportions of the overall diet consisting of aqueous/acidic foods and fatty foods. Consistent with FDA guidelines, a value of 0.667 was used for F_{aq} and 0.333 was used for F_{fat}.

Migration data used for this calculation were selected from Tables 2–6 and correspond to each of the four potential uses for PLA articles: (1) applications involving short-term contact with foods at room temperature or below; (2) intermediate-term contact at room temperature or below; (3) hot food dispensing; and (4) long-term packaging applications. The values used in the calculation of estimated daily intake (EDI) and their sources are described in Table 11. The values were adjusted in the calculation to account for the relative projected market significance of each of the four potential use patterns. It was assumed that 60% of all applications for PLA will involve short-term applications (e.g. houseware applications), 30% will involve intermediate-term applications (e.g. houseware applications where the duration of food contact is between 0.5 hr and 1 day), 5% will involve dispensing hot foods (maximum temperature = 60°C), and 5% will involve longer-term food contact (i.e. food packaging applications).

Using the factors identified above and the values reported in Table 10, the dietary concentration of migrants from PLA is as follows: $0.05 \times 0.1 \times \{(0.667)[(0.6)(1.3) + (0.3)(7.6) + (0.05)(24.3) + (0.05)(11.2)] + (0.333)[(0.6)(0.22) + (0.3)(1.3) + (0.05)(4.0) + (0.05)(9.2)]\} = 0.0180$ parts per million, or 18.0 parts per billion (ppb). The 18.0 ppb figure represents a dietary concentration. This translates to a maximum value of 9 ppb D-lactic acid since this isomer will never be present at a concentration greater than 50% in PLA; usually the concentration will be between 0 and 10% (Gruber *et al.*, 1992).

Actual levels of PLA migrants into the diet will be much lower than 18.0 ppb. The 5% consumption factor grossly exaggerates the projected market volume of PLA. Further, the extraction tests were conducted under conditions that highly exaggerate the time and temperature conditions of food contact and many of the PLA films used in the trials had RLM levels in excess of those that will be found in the commercial product [the commercial product (Gruber *et al.*, 1992) is expected to have an average RLM <0.5% and will never exceed 1%]. Finally, the calculations do not adjust for food handling procedures that will lower the amount of migration. For example, many of the 'intermediate-term' applications will involve refrigeration or freezing of the food after the first hour or two of use, which, based on the temperature dependence of migration, will further reduce the concentration of migrants.

Toxicological aspects

The acute oral toxicity of lactic acid (isomer not indicated) has been determined in several animal species: the LD_{50} in rats was 3.73 g/kg, and in guinea pigs it was 1.81 g/kg (Smyth *et al.*, 1941); in mice it was 4.88 g/kg (JECFA, 1966). An unpublished acute oral toxicity test of the monomer lactide in rats showed an LD_{50} more than 5 g/kg (S. M. Glaza, personal communication, Hazleton Wisconsin, Madison, WI, USA). Thus, lactide has very low intrinsic toxicity and is ultimately converted to lactic acid, which also has very low toxicity.

There are no long-term feeding studies with lactic acid, and only a few short-term studies in animals (Select Committee on GRAS Substances, 1978), but the amount of lactic acid consumed regularly as a natural constituent of foods without signs or symptoms indicates that it must have low toxicity with chronic administration. Lactic acid has been used for medicinal purposes in the form of oral calcium lactate to supply needed calcium in doses of 1–5 g, three

times a day for adults, without adverse effects (*United States Dispensatory*, 1973).

Lactic acid and calcium lactate were not mutagenic in the *in vitro* assays using *Saccharomyces cerevisiae*, or in the Ames test with several strains of *Salmonella typhimurium*, with and without metabolic activation, with mouse, rat and monkey liver microsomes (Litton Bionetics, Inc., 1976a,b).

Lactic acid is a chiral acid. The two stereoisomers are metabolized in different manners in man, although both enantiomers can be transported across the placental barrier in the guinea pig (Girard and Gros, 1980) and across the human placenta (Illsley *et al.*, 1986). L(+)-Lactic acid is a common compound of intermediary metabolism in mammals that is formed by the utilization of glycogen for energy in muscle. L(+)-Lactic acid is then oxidized to pyruvic acid in the liver by L-lactic acid dehydrogenase.

The other stereoisomer, D(−)-lactic acid, is also absorbed from the intestinal tract, but it is poorly metabolized by man. Man and most other mammals do not have a D-lactic acid dehydrogenase, so this isomer is not utilized as a source of energy. Thus, it can accumulate in cells to produce an organic acidosis. It can penetrate tissues such as the brain and interfere with its normal metabolic processes. As a result of this possible effect, the FDA placed a restriction on the use of lactic acid in infant formula, as noted above. The production of the systemic acidosis would require an intake of the D-isomer sufficient to lead to its accumulation and exceed the metabolic capacity to remove it. This requires levels of D(−)-lactic acid much higher than those found in migration from PLA, as discussed below.

In assessing the safety of lactic acid, we have reviewed all the current literature on lactic acid covering the time period from the SCOGS Report in 1978 to the present. Considerable literature on the metabolic effects of D-lactic acid has been published, and is summarized in the remainder of this section.

D(−)-Lactic acid is not known to be produced or metabolized by humans, but it is synthesized by certain micro-organisms that may inhabit the human gastro-intestinal tract. In normal subjects, this does not appear to pose problems, but certain medical conditions (e.g. surgical reduction of the small intestine) can result in increased synthesis and/or absorption of D(−)-lactic acid from the gut (Flourie *et al.*, 1990; Oh *et al.*, 1979; Schoorel *et al.*, 1980; Stolberg *et al.*, 1982). Patients with blood levels of D(−)-lactic acid greater than 0.5 mM display symptoms of metabolic acidosis, hyperventilation, cerebral dysfunction and other medical disorders (Girard and Gros, 1980; Gorman *et al.*, 1990; Thurn *et al.*, 1985). Excessive accumulation of D(−)-lactic acid can pose problems for patients dialysed with solutions containing D(−)-lactic acid at concentrations 10 times greater than that found in serum.

Similar symptoms may occur in ruminant animals fed easily fermented carbohydrates. Such diets induce changes in microflora favouring excessive production of D(−)-lactic acid (Dunlop and Hammond, 1965). Cats fed propylene glycol, which is metabolized to D- and L-lactic acids, display symptoms of acidosis (Christopher *et al.*, 1990). Although these conditions are of medical and/or veterinary importance, they are not directly relevant to the safety of PLA. Consumer exposure to D(−)-lactic acid from intended PLA use is several orders of magnitude lower than the levels shown to cause medical problems.

Healthy adult volunteers fed yogurt containing D(−)-lactic acid (1.06 mmol/kg body weight) exhibited a slight increase in plasma D(−)-lactic acid, from 0.070 ± 0.020 to 0.200 ± 0.010 mmol/litre at 1 hr (de Vrese and Barth, 1991). At lower levels of D(−)-lactic acid consumption (0.64 mmol/kg body weight) the plasma level reached 0.086 ± 0.030 mmol/litre. The authors conclude that consumption of foods containing D(−)-lactic acid may be regarded as safe for healthy adults.

Oral intake of approximately 1 mmol/kg body weight (90 mg/kg) appears to produce only slight increases in plasma concentrations of D(−)-lactic acid. Hence, the special circumstances under which D(−)-lactic acid intake induces adverse effects on acid–base balance and cerebral function are cleary dose dependent and of no relevance to intended PLA use. The very small increase in lactic acid intake that will occur from PLA will not induce these effects or conditions.

Conclusion

The calculated 0.0180 ppm dietary concentration of lactic acid from all proposed uses of PLA as an indirect food additive translates to not more than 0.054 mg/day/person. This represents less than 0.25% of the current intake of lactic acid from all sources of lactic acid added directly to foods. If the amount of lactic acid consumed as a natural component of several common foods is also considered, the very slight additional increment of lactic acid that would result from the proposed uses of PLA as an indirect food additive becomes even smaller. As a final comparison, the projected intake of lactic acid from PLA is approximately 700 times less than the estimated lactic acid intake of breast-fed infants.

Any dietary contribution resulting from the intake of potential migrants from PLA other than lactic acid (i.e. dimers, trimers, etc.) will, in total, represent very small, safe amounts. Migrating quantities of these species will hydrolyse to lactic acid in the aqueous and acidic media commonly found in foods and in the stomach. Moreover, lactide (the cyclic dimer) has demonstrated low intrinsic toxicity in testing. The safety of lactoyllactic acid (the linear dimer) and other higher-order species is evidenced by the fact that they are normally present in commercially available lactic acid (Informatics, Inc., 1975).

A review of the current toxicological literature on lactic acid, particularly covering the period of time since the GRAS status of lactic acid was reviewed in 1978, reveals no cause for concern about the safety of lactic acid added to foods.

In summary, our assessment is as follows:

1. Very limited migration can be expected from PLA into foods that it contacts during intended conditions of use.
2. The small amount of any material that might migrate from PLA into food will be lactic acid, or its dimers and oligomers, which will hydrolyse in aqueous systems to lactic acid.
3. Lactic acid is a common food ingredient that has been shown to be safe in food at levels far in excess of any small amount that might result from the intended uses of PLA.

Based on these findings, we conclude that PLA is safe and Generally Recognized As Safe for its intended uses in fabricating articles intended for use in contact with food.

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