EVALUATION OF THE HEALTH ASPECTS OF LACTIC ACID
AND CALCIUM LACTATE AS FOOD INGREDIENTS

1978

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

Contract No. FDA 223-75-2004
EVALUATION OF THE HEALTH ASPECTS OF LACTIC ACID
AND CALCIUM LACTATE AS FOOD INGREDIENTS

1978

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

Contract No. FDA 223-75-2004

Life Sciences Research Office
Federation of American Societies
For Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshaling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>II. Background information</td>
<td>2</td>
</tr>
<tr>
<td>III. Consumer exposure data</td>
<td>3</td>
</tr>
<tr>
<td>IV. Biological studies</td>
<td>6</td>
</tr>
<tr>
<td>V. Opinion</td>
<td>12</td>
</tr>
<tr>
<td>VI. References cited</td>
<td>14</td>
</tr>
<tr>
<td>VII. Scientists contributing to this report</td>
<td>20</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

This report concerns the health aspects of using lactic acid and calcium lactate as food ingredients. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1973. To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; recent literature searches by the Toxicology Information Response Center, Oak Ridge, Tennessee; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, an announcement was made in the Federal Register of February 17, 1978 (43 FR 7036-7038) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using lactic acid and calcium lactate as food ingredients. The Select Committee received no requests for such a hearing on lactic acid and calcium lactate but received one letter (2) submitted in lieu of a request for a hearing.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarking clearance that is required for food additives. It is stated in the Code of Federal Regulations (3) [21 CFR 170.3 and 170.30] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA (3) recognizes further that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document (PB-241 958/8) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Committee, there are insufficient data upon which to base a conclusion. The Committee is aware that its conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on lactic acid and calcium lactate and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Lactic acid is widely distributed as a metabolic product in living cells. Normal human blood contains 8 to 17 mg per 100 ml of plasma (4). Among the many foods in which lactic acid occurs naturally are meats, fruits, tomato juice, beer, wine, molasses, and sour milk (5).

Chemically, lactic acid is 2-hydroxypropionic acid (CH₃CHOHCOOH). It is a viscous, nonvolatile liquid at room temperature, soluble in water and miscible in alcohol. The calcium salt is a white to cream colored, nearly odorless, crystalline powder with the formula Ca(CH₃CHOHCOO)₂·x H₂O, where x is any number up to 5. It is soluble in water and practically insoluble in alcohol (6).

Both lactic acid and its calcium salt occur as the optically active L(+) or D(−) isomers or as the racemic (DL) mixture of the two. The compound added to foods in the United States is the racemic (DL) form. Commercially, DL-lactic acid is produced synthetically or by Lactobacillus fermentation of sugars, principally corn sugar. In the latter process the fermentation product is neutralized with calcium carbonate, the resultant calcium lactate is purified by recrystallization, and lactic acid is recovered through decomposition with sulfuric acid (7). The optically active L(+) and
D(-) forms can be produced by chemical resolution of the racemic mixture or by selective fermentation using certain Lactobacilli. While many Lactobacilli produce DL-lactic acid, others are known to produce D(-) lactic acid and/or products that consist mainly of L(+) lactic acid with varying small amounts of D(-) lactic acid (8).

The Food Chemicals Codex (6) specifies that food grade lactic acid should contain not less than 95.0 percent or more than 105.0 percent of the labeled concentration, and not more than 0.003 percent arsenic, 0.2 percent chloride, 0.001 percent iron, 0.25 percent sulfate, and 0.001 percent heavy metals (as lead). The Codex specifies that food grade calcium lactate should assay not less than 98.0 percent and not more than 101.0 percent after drying, and contain not more than 0.0003 percent arsenic, 0.45 percent acidity as lactic acid, 0.0015 percent fluoride, 1 percent magnesium and alkali salts, 0.002 percent heavy metals (as lead), and 0.001 percent lead. The isomeric form is not specified for either the acid or the calcium salt but the food grade of each is presumed to be the racemic mixture (7).

Those responding to a survey of the food industry made by a National Research Council (NRC) subcommittee in 1970 indicated that lactic acid was first recorded as having been commercially added to foods in 1946 and its calcium salt in 1950 (9).

Federal regulations (3) list lactic acid [21 CFR 182.1061] and calcium lactate [21 CFR 182.1207] as multiple purpose GRAS food substances. Isomeric forms are not specified but presumed to be racemic (DL). In processing foods, lactic acid is used to maintain the clarity of brine in packing Spanish-type olives by inhibiting microbiological spoilage and fermentation, acidify cheese and dried food casein, impart flavor to carbonated fruit juices and frozen desserts, condition dough, solubilize pepper oleoresin, and stabilize certain types of wine. The calcium salt is employed for such purposes as preserving the firmness of apple slices during processing, improving the crispness of canned bean sprouts, inhibiting the discoloration in fruits and vegetables, improving the properties of milk and baked products, and gelling demethylated pectins (7).

III. CONSUMER EXPOSURE DATA

The NRC subcommittee (9) survey of the food industry has provided information on the levels of additions of lactic acid and calcium lactate to foods in several categories (Table I). Based on information supplied by manufacturers who reported adding the substance to at least one food in a category, weighted means were calculated for the addition of lactic acid and calcium lactate to foods in that category. Some representative levels of use are also given in another report of the NRC (10). The NRC subcommittee estimated...
<table>
<thead>
<tr>
<th>Food category</th>
<th>Lactic acid Weighted mean percent</th>
<th>Calcium lactate Weighted mean percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.204</td>
<td>0.010</td>
</tr>
<tr>
<td>Grain products, such as pastas</td>
<td>0.134</td>
<td>0.003</td>
</tr>
<tr>
<td>or rice dishes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fats and oils</td>
<td>0.093</td>
<td>0.005</td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>1.943</td>
<td></td>
</tr>
<tr>
<td>Cheese</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processed fruits, juices and drinks</td>
<td>0.374</td>
<td>0.005</td>
</tr>
<tr>
<td>Meat products</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td></td>
<td>0.104</td>
</tr>
<tr>
<td>Condiments, relishes, salt</td>
<td>0.713</td>
<td></td>
</tr>
<tr>
<td>substitutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft candy</td>
<td>0.008</td>
<td>0.002</td>
</tr>
<tr>
<td>Sugar, confections</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td>0.050</td>
<td></td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>0.073</td>
<td>0.002</td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Snack foods</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>0.002</td>
<td>0.191</td>
</tr>
<tr>
<td>Beverages, alcoholic</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>0.170</td>
<td></td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>0.081</td>
<td></td>
</tr>
<tr>
<td>Hard candy</td>
<td>0.356</td>
<td></td>
</tr>
<tr>
<td>Chewing gum</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>Sugar substitutes</td>
<td></td>
<td>85.0</td>
</tr>
<tr>
<td>Seasonings and flavors</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

Blanks in the table mean that the substance is not added to the foods indicated. Level of addition of lactic acid and calcium lactate is the weighted mean of the levels reported by manufacturers as their usual addition to one or more products in a food category. For discussion of weighted mean see Section X and Exhibit 50 of reference 9.
possible daily average intakes of lactic acid and calcium lactate by age groups from U.S. Department of Agriculture estimates of portion size, Market Research Corporation of America data on frequency of eating foods in the several categories, and the assumption that all foods within a category contain the substances at the level shown in Table I. Daily intake of lactic acid was estimated to be 924 mg and of calcium lactate, 377 mg for those 2 years and older. However, as pointed out by the NRC subcommittee and as explained in Section XI of the NRC subcommittee's report (9), this procedure is likely to lead to estimates of intakes that are overstated, often by considerable margins. Accordingly, the Select Committee has made the following per capita estimate which it believes is more nearly representative of actual intakes.

The total amounts of lactic acid and calcium lactate used for food purposes in the United States in 1970 (Table II) were estimated as 1.15 million kg and 56,000 kg, respectively, resulting in a per capita daily "intake" of about 15 mg of lactic acid and 1 mg of calcium lactate. Because the per capita figures obviously include losses and wastage from production to consumption, they can be taken to represent maximum probable daily intake except for those individuals who may consistently select those foods containing the greatest amounts of added lactic acid or calcium lactate. Infants receiving special formulas containing calcium lactate may also exceed these per capita intakes.

### TABLE II

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative quantities used(^1) 1970/1960</th>
<th>Total quantity used (1970)(^2)</th>
<th>Per capita daily &quot;intake&quot;(^3) mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acid</td>
<td>1.33</td>
<td>1,150,000</td>
<td>15</td>
</tr>
<tr>
<td>Calcium lactate</td>
<td>0.52</td>
<td>56,000</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^1\) Based only on the reports of those respondents to the National Research Council (NRC) survey submitting information for both 1960 and 1970.

\(^2\) Recalculated to 100 percent from survey data estimated by NRC to represent 60 percent of actual usage.

\(^3\) Per capita calculations based on a U.S. population of 205 million.
The Joint FAO/WHO Expert Committee on Food Additives (11-13) set no limits on the addition of lactic acid and calcium lactate to foods in view of the natural occurrence of the acid and its salts. However, the Expert Committee recommended that neither the D-isomer nor the DL-racemic mixture should be added to formulations for infants less than three months of age. This precaution was based on observations that suggest some lack of capacity of young infants to metabolize the D-form (14). The Council of Europe (15) placed a limit of 25,000 ppm of added lactic acid in food but apparently did not consider calcium lactate. The Japanese Standards of Food Additives (16) placed a maximum limit of 10,000 ppm (as Ca) for added calcium lactate as a dietary calcium supplement and no limitations for lactic acid. Both the Council of Europe and the Japanese Standards are silent with respect to the isomeric forms.

IV. BIOLOGICAL STUDIES

Absorption, metabolism, and excretion

Within the body, L(+) lactate is formed primarily from the glycolysis of carbohydrates (17). Kreisberg (18) reported that most of the production of lactate occurs in the muscles, brain, erythrocytes, and skin, while smaller production takes place in the leucocytes, renal medulla, and intestinal mucosa. Lactate is transported to the liver and converted by lactic acid dehydrogenase to pyruvate. Pyruvate, in turn, can be converted into free glucose, stored as glycogen, and utilized in other metabolic transformations.

Animals readily absorb both L(+) and D(−) lactic acid or lactate from the gastrointestinal tract and have the capacity to completely metabolize both the L(+) and D(−) isomers but at different rates. Cori and Cori (19) intubated rats with levorotatory, dextrorotatory, and racemic sodium lactate (currently designated by convention as D(−), L(+) and racemic sodium lactate, respectively) at a level of 1.7 g per kg body weight and measured liver glycogen and urinary lactate in animals sacrificed three hours after dosing. With the L(+) isomer, 39.6 percent of the absorbed dose was converted to glycogen and less than 1 percent was excreted in the urine. Essentially none of the D(−) isomer was converted to glycogen although it was absorbed at the same rate from the intestine as the L(+) isomer; about a third of the absorbed dose of the D(−) lactate was excreted in the urine. With DL-lactate, 24.9 percent of the absorbed dose was converted to glycogen and about 1.6 percent was excreted. Cori and Cori attribute the differences observed to differences in the rates of utilization of the two isomers; the L(+) isomer was found to be utilized about four
times more rapidly than the D(-) isomer. At the relatively high doses used in these experiments the D(-) isomer was being absorbed more rapidly than it was being utilized, accounting for its appearance in relatively large amounts in the urine.

Conant et al. (20) intubated adult rats with DL-sodium lactate containing $^{11}C$ in the carboxyl position and found an average of 20 percent of the administered radioactivity to be expired as CO$_2$ during the 2.5 hours following administration. Doses varied from 30 to 250 mg per rat (260 to 1800 mg per kg body weight).

Craig (21) found that orally intubated sodium DL-lactate was practically completely metabolized in the dog. In another series of experiments, dogs were infused intravenously with lactic acid preparations containing 35 to 71 percent of the L(+) isomer and the amounts of L(+) and D(-) lactic acid in the blood and urine were measured. It was concluded that the rate of utilization of the L(+) isomer is about 1.5 times that of the D(-) isomer.

Drury and Wick (22) injected labeled L(+) or D(-) lactic acid intravenously into eviscerated nephrectomized rabbits where the important metabolizing tissues are heart, brain, endocrines, and muscles of respiration. With the L(+) isomer, the specific activity of the expired carbon dioxide peaked within two hours after administration and decreased rapidly thereafter. With the D(-) isomer the specific activity of the expired carbon dioxide increased slowly and remained elevated for more than five hours. This study indicated that both the L(+) and the D(-) isomers are oxidized but at different rates, the oxidation of the D(-) isomer being the slower.

Giesecke and Fabritius (23) fed adult rats, for one or two days, a diet containing 5 percent calcium sodium DL-lactate and found that only 1 to 2 percent of the ingested D(-) lactate was recovered in the urine. A specific enzymatic assay was used for the D(-) lactate determination. In further experiments, fasted rats were injected intraperitoneally with 247 mg per kg body weight of D(-) lactate containing $^{14}C$-D(-) lactate. Within six hours, 84.4 percent of the injected dose was recovered as expired CO$_2$, 3 percent as D(-) lactate in the urine, and 3 percent as metabolites in the urine, indicating that D(-) lactate was readily oxidized. In identical experiments with rats fed a diet containing 5 percent DL-lactate, 81.9 percent of the injected D(-) lactate appeared in the expired CO$_2$ and 10.2 percent in the urine as D(-) lactate and metabolites.

Using $^{14}C$-lactate (isomer not indicated but presumably DL), Kreisberg (18) reported lactate turnover rate in normal man to be 82 mg per kg per hour or about 140 g per day in an adult, and Searle and Cavalieri (24) reported a turnover value of 95 mg per kg per hour. Similar turnover rates have been found in dogs (25, 26) and sheep (27) using continuously infused L(+)$^{14}C$ lactate. Baumgärtner and Ketz (28) found DL-lactic acid to have a caloric value of 3,638 cal per g.
Acute toxicity

The oral LD₅₀ for lactic acid (purified laboratory preparation, isomer not indicated) was reported to be 3.73 g per kg for rats and 1.81 g per kg for guinea pigs (29). The oral LD₅₀ of lactic acid (isomer not indicated) for mice was reported as 4.875 g per kg (14). The minimum lethal dose of calcium lactate (isomer not indicated), administered intravenously, was reported to be 80 to 160 mg per kg for dogs and 180 to 380 mg per kg for rabbits (30). Fürth and Engel (31) found rats to survive, without damage, subcutaneous doses of 2 g lactic acid (isomer not indicated) per kg daily for 11 days. Durlacher et al. (32) found that gastric intubation of fasted, two to six-day-old rabbits with a single dose of 6 g calcium lactate (isomer not indicated) per kg body weight did not result in lesions in the stomach and intestines examined 48 hours after dosing.

Animal feeding studies

No long-term feeding studies and only the following few short-term feeding studies have come to the attention of the Select Committee.

Jonek (33) observed that the adrenal cortical activity increased in female rabbits consuming 180 mg lactic acid (isomer not indicated) daily in their feed (120 mg per kg per day) for 38 days, although glutamic acid and citric acid at similar levels showed stronger stimulative effects. Fazekas (34, 35) found that rabbits given 100 to 200 mg per kg body weight of lactic acid (isomer not indicated) every other day in the drinking water for over five months, developed enlarged ovaries (weight increase of 125 to 150 percent) and parathyroids (weight increase of 160 to 277 percent). However, similar effects were found to occur with other compounds tested concurrently, at the same dosage levels such as ammonium hydroxide, ammonium phosphate, and acetic acid.

Human studies

In studies on the metabolism of calcium salts, Lieberman (36) observed that the oral administration of a single dose of 10 g calcium lactate (isomeric form not indicated) in 250 ml of water to each of three healthy men resulted in violent abdominal distress, vomiting, and diarrhea. There were no violent reactions when the dose was 5 g.

A human subject consuming 300 ml of a drink containing 2.82 g of lactic acid (isomer not indicated) excreted 20.7 percent of the lactate in the urine within 13 hours. The same subject consuming 250 ml of a 0.5 percent lithium lactate solution (isomer not indicated) corresponding to 1.17 g of lactic acid, excreted 31.7 percent of the lactate in the urine within 12 hours (31).
Medically, calcium lactate is used to supply calcium in doses of 1 to 5 g, three times a day for adults (37).

Durlacher et al. (32) administered by gavage to five newborn and a four-month-old infant, 6 g calcium lactate (isomeric form not indicated) in 10 percent aqueous solution before the morning feeding. Mild diarrhea occurred in three of the infants, but no vomiting. Serum calcium rose significantly, serum protein slightly, and serum phosphorus decreased as the calcium level increased. No other effects were reported.

Lactic acid has been used to acidify infant formulas. Initially, formulas made from fresh cow milk were acidified as a means of reducing curd tension but with improvements in milk processing (e.g. homogenization, evaporation), low curd tension has been achieved without acidification. While formulas acidified with lactic acid are still marketed in Europe and elsewhere, commercially available infant formulas in the United States, as described in the Physicians' Desk Reference, are not acidified (38). However, since acidification of milk inhibits growth of certain microorganisms and may influence the gastrointestinal flora of the infant, the following considerations are relevant.

A large number of studies of the effect of feeding lactic acid acidified formulas have been reported; however, many of these lack appropriate controls or are rather inadequately described (39-47). Results of the more satisfactory studies (those known or believed to concern acidification with DL-lactic acid) are summarized in Table III and studies known or believed to concern acidification with L(+)/lactic acid are summarized in Table IV.

The majority of the studies summarized in Table III concern premature infants. With intakes of DL-lactic acid of 600 mg per kg per day or greater (the only intakes studied), metabolic acidosis and decreased growth rate were generally observed. Although Toussaint and Ozawa (52) did not observe metabolic acidosis in full-term infants fed formulas acidified with DL-lactic acid, other investigators (39, 40, 45) have reported metabolic acidosis in full-term infants fed such formulas. These latter studies are difficult to interpret because of lack of adequate controls.

As may be seen from Table IV, with one exception, metabolic acidosis was not demonstrated in infants fed formulas acidified with L(+) lactic acid. The exception is the report by Ungari et al. (55), in which neither the source of lactic acid nor the dose is specified. However, the lactic acid was produced by fermentation and it seems possible that the organism produced some D(-)/lactic acid. Controls also demonstrated metabolic acidosis but less severe than that of infants fed the acidified formula. Full-term infants were also reported to develop metabolic acidosis when fed this acidified formula (45). Other authors (not cited in Table IV) fed formulas acidified
<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Estimated dose (mg/kg/d)</th>
<th>Duration of treatment (d)</th>
<th>Metabolic acidosis</th>
<th>Decreased growth rate</th>
<th>Comment**</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>875</td>
<td>27</td>
<td>Yes</td>
<td>Yes</td>
<td>Premature infants 8-12 days old, mean weight 1820 g; 10 controls received unacidified formula. Premature infants 8-12 days old, mean weight 1750 g; same infants studied for an average of 21 days with unacidified formula.</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>850</td>
<td>16</td>
<td>Slight</td>
<td>No</td>
<td>&quot;Premature infants,&quot; 12 days old; 25 controls fed unacidified formula; 16 additional premature infants fed formula with 600 mg per kg per day D(-) lactic acid also developed metabolic acidosis.</td>
<td>49</td>
</tr>
<tr>
<td>29</td>
<td>600</td>
<td>12</td>
<td>Yes</td>
<td>Not recorded</td>
<td>&quot;Premature infants,&quot; 12 days old; 25 controls fed unacidified formula; 16 additional premature infants fed formula with 600 mg per kg per day D(-) lactic acid also developed metabolic acidosis.</td>
<td>49</td>
</tr>
<tr>
<td>18</td>
<td>600</td>
<td>7-10</td>
<td>Yes</td>
<td>Yes</td>
<td>Premature infants, 7-56 days old, weight 1219-2180 g; 18 controls fed unacidified formula.</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>1275</td>
<td>7</td>
<td>Yes</td>
<td>Yes</td>
<td>Premature infants, 4-34 days old, weight 1304-1871 g; 6 controls fed unacidified formulas.</td>
<td>50</td>
</tr>
<tr>
<td>14</td>
<td>600</td>
<td>14-36</td>
<td>Yes</td>
<td>Yes</td>
<td>Premature infants, 10 days old, weight 1474 to 1786 g; 30 controls fed unacidified formula.</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>600</td>
<td>14</td>
<td>No</td>
<td>Not recorded</td>
<td>Full-term and premature infants ½ to 3 months old; controls fed unacidified formula.</td>
<td>52</td>
</tr>
</tbody>
</table>

* In some instances it is impossible to be certain that DL rather than L(+)) lactic acid was employed.
** No appropriate separate controls unless specifically noted; in some instances subjects served as own controls but with the possible exception of Ballabriga (48) in no instance was order of treatment randomized or a balanced crossover design utilized.
<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Estimated dose (mg/kg/d)</th>
<th>Duration of treatment (d)</th>
<th>Metabolic acidosis</th>
<th>Comment</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>600</td>
<td>12</td>
<td>No</td>
<td>&quot;Premature infants&quot; beginning at 12 days old; 21 received formula with added L(+) lactic acid, 21 received formula acidified by fermentation; 25 controls fed unacidified formula.</td>
<td>49</td>
</tr>
<tr>
<td>21</td>
<td>880</td>
<td>Not stated</td>
<td>No</td>
<td>&quot;Premature infants&quot; 14 to 70 days old, fed formulas acidified with L(+) lactic acid; 21 controls fed same formula unacidified.</td>
<td>53</td>
</tr>
<tr>
<td>29</td>
<td>810</td>
<td>2-28</td>
<td>No</td>
<td>Normal infants and infants recovering from illness; 29 infants, 2-100 days old fed formula acidified by fermentation*, organism not identified. 24 controls fed unacidified formula.</td>
<td>54</td>
</tr>
<tr>
<td>15</td>
<td>Not stated</td>
<td>15</td>
<td>Slight in both experimental and controls</td>
<td>Premature infants, 6 days old, birth weights 1510-2500 g, fed formulas acidified by fermentation*, organism not identified; 15 controls fed unacidified formula.</td>
<td>55</td>
</tr>
</tbody>
</table>

*No definite evidence that the fermentative organism was one that produces only L(+) lactic acid.
with L(+) lactic acid or acidified "by fermentation" and did not observe metabolic acidosis in premature infants (39, 46) or in "normal" infants or those recovering from illness (43). It is to be noted that concern has also been expressed about the ability of young infants to metabolize the unnatural (D) isomer of malic acid (56).

None of the reports concerning infants fed formulas acidified with L(+) lactic acid or acidified "by fermentation" include data on rate of growth, but the Select Committee considers it unlikely that interference in rate of growth would occur in the absence of metabolic acidosis.

It is to be noted that some special products such as powdered milk formulas containing up to 3 percent lactic acid for dietary management of infants with celiac disease and glucose solutions containing up to 50 mg lactic acid per liter for oral hospital use in initial feedings of premature infants, are produced in the United States (2, 38). Such special products are not being evaluated in this report.

Special studies

Lactic acid, USP, at levels up to 0.18 percent and calcium lactate, USP, at levels up to 0.625 percent did not exhibit mutagenic activity in in vitro microbial assays using strains of Saccharomyces cerevisiae or Salmonella typhimurium, with or without activation with mouse, rat, or monkey liver homogenates (57, 58). Lactic acid, USP (59) is a mixture of lactic acid and lactic acid lactate. It contains the equivalent of 85 to 90 percent lactic acid, is obtained by fermentation of sugar or prepared synthetically, and is probably the racemic (DL) form.

V. OPINION

Lactic acid is produced in varying amounts by most living tissues as a normal metabolic intermediate. The lactate turnover rate in man has been estimated to be of the order of 2 g per kg per day.

An additional load of up to 1 mg per kg per day of lactic acid as the free acid or as calcium lactate contained in commercially prepared food commodities would not appreciably modify the normal metabolic processes. None of the limited toxicity data available raises any suspicion of adverse effects in adults at doses orders of magnitude above the estimated levels of human consumption. There is no indication that the per capita intake of lactate from processed foods will be substantially increased in the foreseeable future.
There is no evidence of potential toxicity of the L-isomer for individuals of any age. However, premature infants fed formulas acidified with DL-lactic acid (or, in one instance, D(-) lactic acid), have reported to develop metabolic acidosis and growth retardation. Results of studies of full-term infants are conflicting and difficult to interpret. Resolution of this conflict is needed even though, as far as the Select Committee is aware, lactic acid acidification of infant formulas is not currently being practiced in the United States except in products designed for special dietary or therapeutic purposes which are not being evaluated in this report.

In the light of these considerations, the Select Committee concludes that:

There is no evidence in the available information on L(+) lactic acid and L(+) calcium lactate that demonstrates or suggests reasonable grounds to suspect a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future.

There is no evidence in the available information on either of the isomers of lactic acid, their calcium salts, and their racemates that demonstrates or suggests reasonable grounds to suspect a hazard to individuals beyond infancy when they are used at levels that are now current or that might reasonably be expected in the future.

The evidence on D(-)-lactic acid, DL-lactic acid and their calcium salts is insufficient to determine that the adverse effects reported would not be deleterious to infants should they be used in infant formulas. Lactic acid acidification of generally available infant formulas is not now being practiced in the United States.
VI. REFERENCES CITED


2. Letter dated March 13, 1978, from H.P. Sarett, Vice President, Nutritional Science Resources and E.H. Stevenson, Director, Regulatory Affairs/ Nutritional Division, Mead Johnson Research Center, Evansville, Ind., to Select Committee on GRAS Substances, Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Md.


VII. SCIENTISTS CONTRIBUTING TO THIS REPORT

1. Members of the Select Committee on GRAS Substances:

Joseph F. Borzelleca, Ph.D., Professor of Pharmacology, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond, Va.

Harry G. Day, Sc.D., Professor Emeritus of Chemistry, Indiana University, Bloomington, Ind.

Samuel J. Fomon, M.D., Professor of Pediatrics, College of Medicine, University of Iowa, Iowa City, Iowa.

Bert N. La Du, Jr., M.D., Ph.D., Professor and Chairman, Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Mich.

John R. McCoy, V.M.D., Professor of Comparative Pathology, New Jersey College of Medicine and Dentistry, Rutgers Medical School, New Brunswick, N.J.

Sanford A. Miller, Ph.D., Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, Cambridge, Mass.

Gabriel L. Plaa, Ph.D., Professor and Chairman, Department of Pharmacology, University of Montreal Faculty of Medicine, Montreal, Canada.

Michael B. Shimkin, M.D., Professor of Community Medicine and Oncology, School of Medicine, University of California, San Diego, La Jolla, Calif.

Ralph G.H. Siu, Ph.D., Consultant, Washington, D.C.

John L. Wood, Ph.D., Distinguished Service Professor, Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tenn.

George W. Irving, Jr., Ph.D., (Chairman), Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Md.
2. LSRO staff:

Kenneth D. Fisher, Ph.D., Director
Frederic R. Senti, Ph.D., Associate Director
C. Jelleff Carr, Ph.D., Director Emeritus
Richard G. Allison, Ph.D., Staff Scientist
Andrew F. Freeman, Senior Staff Scientist
John M. Talbot, M.D., Senior Medical Consultant
Michael J. Wade, Ph.D., Staff Scientist

The Select Committee expresses its appreciation to Clinton Corn Processing Company, Clinton, Iowa 52732, who contributed information and data.

Report submitted by:

May 23, 1978
Date

George W. Irving, Jr., Chairman
Select Committee on GRAS Substances