EVALUATION OF THE HEALTH ASPECTS OF MALIC ACID

AS A FOOD INGREDIENT

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Prepared for

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

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
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 marshalling 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.

C. Jelleff Carr, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This report concerns the health aspects of using malic acid as a food ingredient. 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; 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 13, 1976 (41 FR 6787 and 6788) 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 malic acid as a food ingredient. The Select Committee received no requests for such a hearing on malic acid.

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 21 CFR 121.1, revised April 1, 1975 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. This section of the Code also indicates 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 recognizes further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

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 Select 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 Select Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available

*The document (PB-223 865/7) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Select Committee, there are insufficient data upon which to base a conclusion. The Select Committee, aware that biological testing is dynamic, bases its conclusions on information now available; it cannot anticipate the results of experiments not yet conducted or those of tests that may be reconduted, using new technologies. These 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 malic acid and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Malic acid, 1-hydroxy-1,2-ethanedicarboxylic acid (HOOC·CHOH·CH₂·COOH), is a white crystalline substance containing one asymmetric carbon atom. The natural isomer, L(+), malic acid, referred to as L-malic acid, occurs in a variety of fruits and vegetables as well as in body fluids and tissues where it is an intermediary metabolite in the citric acid cycle. L-malic acid is the principal, or a major organic acid in many common fruits, berries, and vegetables (2,3). Racemic DL-malic acid does not occur naturally, and is made commercially from fumaric and maleic acids.

Malic acid is listed in the Code of Federal Regulations (4) as GRAS for use as a miscellaneous or general purpose food additive [21 CFR 121.101 (d)(8)], where the isomeric form is not specified, and as a synthetic flavoring substance [21 CFR 121.101 (g)], where the isomer is specified. Two 1965 publications (5,6) list L-malic acid as a flavoring agent. However, essentially all the malic acid added to foods in the United States is the synthetic racemic DL-malic acid (3).

The Food Chemicals Codex (7) specifies that food grade DL-malic acid contain not less than 99.5 percent of C₄H₆O₅ and, for the following listed impurities, not more than: 3 ppm arsenic, 10 ppm lead; 20 ppm heavy metals (as lead); 0.5 percent fumaric acid; and 0.05 percent maleic acid. Malic acid is used as an acidulant in nonalcoholic beverages, jams, jellies, preserves, sherbets, and candy (3) and in other food categories. It was reported to have been first used as a food additive in the United States in 1930 (8).
In 1965 the Joint FAO/WHO Expert Committee on Food Additives recommended a conditional acceptable daily intake of D-malic acid of 100 mg per kg body weight, but no limit was suggested for L-malic acid (9). It was stated that the enzyme responsible for conversion of the D- to L-isomers of lactic and malic acids is relatively deficient in very young infants; some concern was expressed that D-lactic acid might be toxic in early infancy and that presumably this might also apply to D-malic acid. In 1969, (10), and in the most recent of their reports that consider malic acid, the FAO/WHO Committee concluded on the basis of further evidence that adults should be able to metabolize D-lactic and D-malic acids and the conditional acceptable daily intake limit of D-malic acid was removed in favor of limits based upon good manufacturing practice. However, the restrictions against the use of D-lactic and D-malic acids in the diets of very young infants was retained.

III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (NRC) surveyed manufacturers by questionnaire concerning the usual and maximal addition of malic acid to foods (8). Based upon information supplied by those manufacturers who reported adding the substance to at least one food in a category, a weighted mean was calculated for the usual and maximal addition of the substance to foods in the category. Weighted means of the usual levels of addition of malic acid are included in Table 1.

The NRC subcommittee estimated the possible average daily intake (Table II) from Market Research Corporation of America data on the mean frequency of eating foods by food category, U.S. Department of Agriculture data on mean portion size of foods in these categories, and the assumption that all food products within a category contained malic acid at the levels shown in Table I. Such an assumption is likely to lead to overestimates of intake. The Select Committee has converted these estimates to possible intakes per kilogram of body weight. The NRC subcommittee has estimated the possible average daily malic acid intake from added sources on the basis of these data, and has recognized that in most cases its calculations of possible intakes are overstated, often by considerable margins.*

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (8). The Select Committee finds this explanation reasonable, and concurs in the first recommendation in Section XII of the same report that, "In order to conduct a more accurate survey of the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
<table>
<thead>
<tr>
<th>Food category</th>
<th>Weighted mean percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft candy</td>
<td>2.50</td>
</tr>
<tr>
<td>Chewing gum</td>
<td>0.74</td>
</tr>
<tr>
<td>Jams, jellies, sweet spreads</td>
<td>0.38</td>
</tr>
<tr>
<td>Processed fruits, juices, and drinks</td>
<td>0.22</td>
</tr>
<tr>
<td>Sugar, confections</td>
<td>0.17</td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>0.10</td>
</tr>
<tr>
<td>Beverages, alcoholic</td>
<td>0.16</td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td>0.12</td>
</tr>
<tr>
<td>Fats and oils</td>
<td>0.10</td>
</tr>
<tr>
<td>Hard candy</td>
<td>0.10</td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>0.08</td>
</tr>
<tr>
<td>Meat products</td>
<td>0.05</td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>0.05</td>
</tr>
<tr>
<td>Instant coffee, tea</td>
<td>0.02</td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td>0.02</td>
</tr>
<tr>
<td>Snack foods</td>
<td>0.01</td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td>0.01</td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>0.01</td>
</tr>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.01</td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Level of addition of malic acid 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 8.
TABLE II

Possible Average Daily Intake of DL-Malic Acid by Age Group (8)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Intake mg</th>
<th>Intake mg/kg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 mo</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>6-11 mo</td>
<td>284</td>
<td>35</td>
</tr>
<tr>
<td>12-23 mo</td>
<td>463</td>
<td>42</td>
</tr>
<tr>
<td>2-65+ yrs</td>
<td>746</td>
<td>12</td>
</tr>
</tbody>
</table>

*Calculation of mg per kg of body weight was based on an average weight of 60 kg for an adult (I1) and the following estimated weights of infants by age groups: 0-5 mo, 5 kg; 6-11 mo, 8 kg; 12-23 mo, 11 kg (I2).

Because of factors detailed in Section XI of the subcommittee's report, they stated that the average estimated total dietary intakes are likely to be much higher than would be the intakes achieved through consumption of a diet consisting totally of processed foods to which the substance had been added at maximum levels. Therefore, higher estimates of intake made by the subcommittee are not reproduced in this report. The Select Committee believes that the average intakes calculated by the NRC subcommittee (Table II) could be achieved by only a small fraction of the population.

Such estimates should be viewed in the light of the total amount of malic acid used in foods (Table III). Calculation of per capita daily consumption on this latter basis suggests a possible average daily intake of approximately 42 mg, a much lower exposure than is implied by the data in Table II. The Select Committee regards the figures in Table II as greatly in excess of the levels likely to be achieved by any of the age groups, and considers 42 mg per capita per day to be a more reasonable estimate. The Select Committee assumes that Table II contains overestimates of intakes of malic acid in all age groups.

Comparison of the total amount of malic acid added to foods in 1960 with the amount reported for 1970 shows an increase of about eightfold. Whether this represents a greater number of foods with added malic acid or an increase in the amounts added to specific foods could not be determined from the information available to the Select Committee.

Half of the daily per capita intake of 42 mg of the racemic DL-malic acid is the L-isomer, which should be compared with an estimate of 1.5 to 3 g for the average daily consumption of L-malic acid from natural food sources (13). Assuming this estimate reasonable for the current food
TABLE III
Consumption of DL-Malic Acid Based on Total Quantity
Used Annually in Foods (8)

<table>
<thead>
<tr>
<th>Relative amounts used(^1)</th>
<th>Total used (1970)(^2)</th>
<th>Per capita daily intake(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970/1960</td>
<td>3,200,000 kg</td>
<td>42 mg</td>
</tr>
</tbody>
</table>

\(^1\)Based only on the reports from those respondents to the National Research Council survey who submitted information for both 1960 and 1970 (8).
\(^2\)Total is the sum of NRC and Flavor and Extract Manufacturers' Association (FEMA) usage data recalculated to 100 percent from survey data that the NRC subcommittee estimated to represent about 60 percent of the actual usage.
\(^3\)Based on total consumption, 1970, and a U.S. population of 205 million.

content of malic acid, the increment of added L-malic acid would represent a very small increase in total daily intake. However, since all malic acid added to foods is DL-malic acid which is half D-malic acid, an evaluation of the health aspects of malic acid requires that particular attention be given the D-isomer alone or as a component of the racemic mixture added to foods.

IV. BIOLOGICAL STUDIES

The metabolism of L-malic acid has been extensively investigated and is well documented in the biochemical literature (1). L-malic acid is synthesized via condensation of acetyl-CoA and glyoxylate and is oxidized to oxaloacetate in the Krebs cycle. Malic dehydrogenase, malic oxidase, and certain other enzymes of intermediary metabolism are specific for L-malic acid. However when grown on media containing D-malate, Escherichia coli can be induced to develop a D-malic acid enzyme which catalyzes an oxidative decarboxylation of D-malate to pyruvate and carbon dioxide (14). D-malic acid inhibits the soluble (non-mitochondrial) L-malic dehydrogenase, but a high D-malate/L-malate ratio is needed for a pronounced effect (15).
The fate of D-malic acid in mammals is not known. DL-malic acid given parenterally to rabbits and dogs resulted in the urinary excretion of D-malic acid (16). Incubation of DL-malic acid with muscle preparations in vitro showed that the L-isomer was preferentially metabolized (17). Although DL-malic acid added to diets low in carbohydrates resulted in increased liver glycogen of rats, the contribution of the D-isomer was not determined (18).

Relatively few studies are available in which the biological effects and toxicity of the D- and L-isomers of malic acid were compared, and unfortunately, in many studies of malic acid, the authors do not specify whether L-malic or DL-malic acid was used. Malic acid as a 0.25 N solution given intravenously to rabbits in a dose of 2.49 g per kg was acutely lethal (19). Intraperitoneal L-malic acid in rats at 1 g per kg was not lethal, but the same dose of D-malic acid killed rats within 20 to 25 minutes (20). DL-malic acid given subcutaneously to one rabbit in large amounts (3 g followed the next day by 1.5 g, and 1.5 g two days later with sacrifice four hours after the last dose) produced small areas of hemorrhage in the renal cortex, limited tubular degeneration, and some glomerular obliteration (21). Two other rabbits receiving similar subcutaneous doses showed increases in blood nonprotein nitrogen and decreases in phenolsulphonephthalein elimination rate. The authors considered that DL-malic acid was slightly nephrotoxic to rabbits. In view of the known nephrotoxicity of maleic acid (22), it is possible that the renal pathology could have been due to maleic acid residual from the preparation of DL-malic acid employed in these studies.

Rabbits receiving cholesterol, 70 mg per kg daily, were given malic acid intraperitoneally, 300 mg twice a week for five months. Animals receiving both malic acid and cholesterol developed twice as high blood cholesterol levels as did those receiving only cholesterol. No hypercholesterolemia resulted in a control group given malic acid without added dietary cholesterol, but degeneration of elastic fibers and the accumulation of acid mucopolysaccharides in the aorta, with atherosclerotic changes in the aortic wall, were noted. Similar pathological changes were noted in rabbit aortas when cholesterol feeding was combined with citric or fumaric acids, suggesting that these agents had similar deleterious effects (23).

When albino rats of the Charles River strain were fed DL-malic acid in the diet for 104 weeks at levels of 0.05, 0.5 and 5.0 percent, no significant pathology was noted (24). Beagle dogs fed diets with the same levels of added DL-malic acid for 104 weeks also showed no gross or microscopic pathological changes due to the consumption of DL-malic acid (25). The malic acid intake levels from these diets would be approximately 2, 20, and 200 mg per kg per day for rats after the eighth week, and 14, 140,
and 1,400 mg per kg per day for the dogs. There were significant reductions in food consumption and weight gain in both male and female rats during the first year of receiving the highest malic acid diets, but no significant differences during the second year. Hematological, blood chemistry, and urine analyses did not show any compound-related effects in either rats or dogs. Male and female rats from all experimental and control groups primarily among those receiving the highest dosage of malic acid, exhibited hunched appearance and/or alopecia during the first year. In the second year, these signs were observed in most animals from all groups. Protruding eyes were noted in six male rats in the highest dosage group during the second year, but not in males of any other group. A few females from each test group and the controls also showed protruding eyes during the second year. Some organ weight and organ/body weight ratio variations of thyroid gland, heart, liver, spleen, kidneys, and testes were observed in male and female rats of the 5 percent dietary level groups. None of these changes was considered clearly related to malic acid intake and the gross and microscopic examinations revealed no histopathology or trends suggesting a direct relationship to the dose of malic acid ingested (24).

After either oral or intraperitoneal administration of doses of 2.5 mg per kg of L- or [14C] DL-malic acid to rats, both forms were largely oxidized to carbon dioxide and less than 10 percent of the radioactivity was excreted in the urine (26). The author concluded that there should be no justification for discriminating against the use of D-malic acid as a food additive because the two preparations were metabolized at the same rate. However, the doses used were relatively low, and it is possible that a limited capacity to metabolize D-malic acid might not have been detected by these experiments.

The injection of 1 mg of L-, or DL-malic acid into the yolks of chicken eggs showed a small but statistically significant increase in rumplessness (4.3 ± 1.0 percent with L-malic acid and 3.9 ± 1.0 percent with DL-malic acid) over the controls (1.3 ± 0.5 percent). Injection of the D-isomer had no significant effect on the occurrence of rumplessness (27).

The permeability of mouse embryos to L-malic acid was studied by Wales and Biggers (28). Uniformly labeled [14C] L-malic acid did not enter 2-cell embryos; the 8-cell embryos accumulated the labeled substrate and were able to convert some to CO2. The data also suggested that the uptake of L-malic acid was by an active transport process.

In a reproduction study in rats, DL-malic acid added at levels of 0.1 and 1.0 percent of the diet (estimated intakes approximately 4 and 40 mg per kg per day) was fed for nine weeks before mating of the $P_1$ generation and continued through the sacrifice of the $F_2$ pups at weaning. The appearance and behavior of the parental animals and their pups were generally
comparable with the controls throughout the study. Reproduction indices of the test animals were similar to those of the controls. The F₂ fetuses delivered by Caesarean section showed no significant differences between the test and control groups in the number and placement of implantation and resorption sites, or the number, length and weight of the live fetuses. There were no dead fetuses, and no skeletal abnormalities or differences in skeletal development between the test and control fetuses (29).

Teratologic studies have been made on pregnant mice and rats following the oral administration of DL-malic acid (30, 31). Commencing on day 6 of gestation, daily doses by intubation of up to 266 mg per kg for 10 days in mice, and up to 350 mg per kg for 10 days in rats had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities in either soft or skeletal tissues of test animals did not differ from those occurring spontaneously in vehicle-treated controls.

Malic acid (isomeric form not indicated) did not show teratogenic activity when aqueous solutions were injected at levels of 100 to 200 mg per kg into the air cells or yolks of unincubated eggs and eggs after 96 hours of incubation. The LD₅₀ of malic acid was estimated to be 230 mg per kg upon air cell injection in unincubated eggs; 8 mg per kg upon air cell injection after 96 hours of incubation (32).

Mutagenicity tests of DL-malic acid were conducted using Salmonella typhimurium and Saccharomyces cerevisiae microbial assays and without the addition of mammalian metabolic enzyme preparations (33). DL-malic acid did not exhibit any mutagenic activity under the conditions employed in this in vitro evaluation.

No information on possible carcinogenicity of L-, D-, or DL-malic acid was available to the Select Committee.

V. OPINION

In view of the natural occurrence of L-malic acid in a variety of fruits, vegetables, and certain other foods, its important role in intermediary metabolism as a component of the Krebs cycle, rather detailed knowledge of its formation and metabolism in animals and plants, its relatively low toxicity when given orally to animals, and its specialized uses in foods and nonalcoholic beverages as an acidulant or flavoring agent, there is no scientific basis for suspecting that the amounts of L-malic acid now added to foods would be hazardous. There is no indication that malic acid is added to any foods specifically designed for infant feeding.
The scientific literature is less satisfactory on D-malic acid, the unnatural isomer, and a co-constituent of the racemic DL-malic acid, which is the form now used as a food additive. Very little is known about the metabolism, absorption, excretion, and biological effects of D-malic acid, or whether animal species differ in the way they can utilize and tolerate this compound. DL-malic acid was employed in several of the toxicological, reproductive, and teratological studies; results suggest that D-malic acid, as a component of DL-malic acid, is not likely to have adverse effects. Some concern has been expressed about the ability of young infants to metabolize D-malic acid, but fortunately, in current practice, this does not pose a problem since DL-malic acid is not now added to infant foods.

The Select Committee has weighed the foregoing and concludes:

For individuals beyond the age of infancy, there is no evidence in the available information on L-malic acid and DL-malic acid 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.
VI. REFERENCES CITED


20. Stern, J. R., Professor and Chairman, Brookdale Dental Center of New York University, College of Dentistry, Department of Biochemistry, New York, N. Y. Letter dated December 12, 1973 to Dr. Bert N. La Du, Jr.


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June 2, 1976
Date

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