EVALUATION OF THE HEALTH ASPECTS OF
GLUCONO DELTA-LACTONE AS A FOOD INGREDIENT

1981

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health and Human Services
Washington, D.C.

Contract No. FDA 223-78-2100
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
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NOTICE

This report, one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior-sanctioned food substances as food ingredients, is being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-78-2100 with the Food and Drug Administration (FDA), U.S. Department of Health and Human Services. 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 Dockets Management Branch, 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
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## 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>4</td>
</tr>
<tr>
<td>IV. Biological studies</td>
<td>5</td>
</tr>
<tr>
<td>V. Opinion</td>
<td>8</td>
</tr>
<tr>
<td>VI. References cited</td>
<td>9</td>
</tr>
<tr>
<td>VII. Scientists contributing to this report</td>
<td>13</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

This report concerns the health aspects of using glucono delta-lactone as a food ingredient. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (Dailey, 1978), which summarizes the world's scientific literature from 1920 through 1978. To ensure 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 April 21, 1981 (46 FR 22810-22814) 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 glucono delta-lactone as a food ingredient. The Select Committee received no request for a hearing.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premartketing clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (Office of the Federal Register, 1980a) [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 recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO reviewed and evaluated the available information on glucono delta-lactone in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Committee, in accordance with FDA's guidelines, relied primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. This report is intended for the use of FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act. The Committee anticipates that its conclusions will be reviewed as new information becomes available.
II. BACKGROUND INFORMATION

Glucono delta-lactone (C\textsubscript{6}H\textsubscript{10}O\textsubscript{6}), molecular weight 178.14, is an inner ester of gluconic acid. Commonly named gluconolactone, other synonyms include D-gluconic acid delta-lactone, D-glucono-1, 5-lactone, and D-delta-gluconolactone. Some of its earliest uses as a food ingredient were as a flavoring (e.g. sherbets) and to reduce fat absorption in doughnuts and cones (Feldberg, 1959a). Glucono delta-lactone tastes sweet initially and has a slightly acid aftertaste. The unpublished GRAS uses of glucono delta-lactone are as a buffer or neutralizing agent (Cassidy, 1960), an acidulant (Cassidy, 1961), and a leavening agent (Beebe, 1963; Wulfsberg, 1960). It may also be used at a level up to 8 oz/100 lb of product as an accelerator of color fixing in comminuted meat or meat food products under the provisions of 9 CFR 318.7 (Office of the Federal Register, 1980b). A survey of food processors has shown that glucono delta-lactone is added to foods in several food categories for pH control, leavening, and curing (Subcommittee on Review of the GRAS List--Phase II, 1972).

Glucono delta-lactone is prepared commercially by the oxidation of glucose with bromine water (The Merck Index, 1976). It is available commercially as a white, crystalline powder that is soluble in water (59 g/100 ml), slightly soluble in alcohol (1 g/100 g), and insoluble in ether (The Merck Index, 1976). The Food Chemicals Codex (National Research Council, 1981) specifies that food grade glucono delta-lactone shall assay not less than 99.0\% C\textsubscript{6}H\textsubscript{10}O\textsubscript{6} and have limits on impurities of not more than 0.002\% heavy metals (calculated as Pb), 10 ppm Pb, 3 ppm As, and 0.5\% reducing substances (calculated as D-glucose). An acceptable daily intake (ADI) for total gluconates (calculated as gluconic acid and including glucono delta-lactone) has been set at 50 mg/kg body wt (Food and Agriculture Organization of the United Nations, 1967; Codex Alimentarius Commission, 1975).

In cold water, glucono delta-lactone hydrolyzes slowly to an equilibrium mixture of gluconic acid (55-60\%) and its delta- and gamma-lactones (40-45\%). Pocker and Green (1973) described the kinetics of this hydrolysis, pointing out that little gamma-lactone would be produced prior to establishing the delta-lactone--gluconic acid equilibrium under their test conditions, 0.05 M solution in 0.60 M acetate buffer (pH 4.63). Within 2 h, the pH of a freshly prepared 1\% aqueous solution decreases from about 3.6 to 2.5 (The Merck Index, 1976). Tharandt et al. (1979) measured 75\% hydrolysis of the lactone 5 h after dissolving 200-400 g of glucono delta-lactone in a liter of room temperature water; hydrolysis could be limited to 48\% by addition of appropriate buffering agents. As the acidulant component of a leavening formulation, glucono delta-lactone yields gluconic acid at an accelerated rate as the temperature or concentration is increased during processing and baking.
operations (Feldberg, 1959b). The stability of glucono delta-lactone in dry bakery mixes may be increased and the quality of the final baked product improved by coating the dry glucono delta-lactone with calcium stearate (Feldberg, 1959b) or vegetable oil (Larsen, 1961).

The use of glucono delta-lactone with nitrates in processed meats has bacteriostatic and color stabilizing effects that are favorably enhanced by the mild acidity imparted by gluconic acid. A low pH also increases water-binding capacity and emulsifying qualities of meat protein (Mol and Timmers, 1970; Pate et al., 1971; Riemann et al., 1972). The predictable release of gluconic acid from glucono delta-lactone has been employed successfully for the coagulation of milk in cheese production, particularly cottage cheese (Deane and Hammond, 1960).
III. CONSUMER EXPOSURE DATA

In a National Research Council survey of the food industry's GRAS food ingredient usage in 1970, eight companies reported a total usage for glucono delta-lactone of 44,000 kg (Subcommittee on Review of the GRAS List--Phase II, 1972). The survey coverage was estimated as about 60%. If allowance is made for extent of coverage, the annual usage was about 73,000 kg and the per capita daily disappearance of glucono delta-lactone in 1970 was about 0.9 mg (about 15 μg/kg body wt for a 60-kg adult). The levels of addition of glucono delta-lactone to products in several categories of food are listed in Table 1. Many products in these food categories do not contain added glucono delta-lactone. Moreover, when added, much of the glucono delta-lactone is converted to gluconate during processing.

Table 1. Levels of Addition of Glucono Delta-Lactone to Foods by Food Category (Subcommittee on Review of the GRAS List--Phase II, 1972).

<table>
<thead>
<tr>
<th>Food Category</th>
<th>Weighted Mean Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.31</td>
</tr>
<tr>
<td>Milk products</td>
<td>1.01</td>
</tr>
<tr>
<td>Cheese</td>
<td>1.00</td>
</tr>
<tr>
<td>Processed fruits, juices, and drinks</td>
<td>0.25</td>
</tr>
<tr>
<td>Meat products</td>
<td>0.15</td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>0.20</td>
</tr>
</tbody>
</table>
IV. BIOLOGICAL STUDIES

Phosphorylated derivatives of glucono delta-lactone and gluconic acid, the hydrolysis product of glucono delta-lactone, are intermediates in glucose metabolism in the pentose phosphate shunt. After intraperitoneal administration of radiolabeled sodium gluconate to adult male rats, gluconate carbon was incorporated into both nucleic acid and glycogen by a "more or less direct conversion of gluconic acid into glucose" (Stetten and Stetten, 1950). Studies by Eyles and Lewis (1943) showed glucono delta-lactone was almost as effective as glucose in promoting growth and development of young albino rats. Tharandt et al. (1979) found that $^{14}$C-labeled glucono delta-lactone intubated into normal or alloxan-diabetic rats (0.8 g/kg) was absorbed more rapidly than sodium gluconate as judged by the rate and amount of radioactivity detected in blood within 5 h after administration of the test substance. However, gluconate and its lactone appeared to be metabolized to similar extents within 8-9 h. The Select Committee (SCOGS, 1975; 1978; 1979a, b; 1980a, b) has evaluated the health aspects of several gluconate salts and found no cause for concern relative to the occurrence of gluconate ion in those GRAS ingredients. Experimental findings reviewed in the following sections include those available on glucono delta-lactone as well as selected material concerning gluconic acid.

Glucono delta-lactone was reported to inhibit competitively mannosidase and glucosidase isolated from rat epididymis and limpet tissue (Levvy et al., 1964). Palmer (1971) confirmed these findings using acid alpha-glucosidase from rabbit. Tu et al. (1971) reported that glucono delta-lactone is a noncompetitive inhibitor of polysaccharide phosphorylase in in vitro assays. The enzyme gluconolactonase (E.C. 3.1.1.17) has been isolated from porcine liver by Roberts et al. (1978) and found to catalyze the hydrolysis of glucono delta-lactone to gluconic acid with maximum activity at pH 7.5.

Acute toxicity

Chenoweth et al. (1941) administered orally, water solutions containing up to 500 mg of glucono delta-lactone/kg body wt to men. When three men were given 10 g (about 160 mg/kg) of glucono delta-lactone orally as a 10% solution, the amounts recovered in the urine in 7 h represented 7.7-15% of the dose. When 5 g (84 mg/kg) was given orally, none was recovered in the urine. Doses of 15 g glucono delta-lactone administered orally frequently caused abdominal cramps and diarrhea in the subjects of this study and in the earlier study of Gold and Civin (1939).
Short-term toxicity

After administering 1.0 g of gluconic acid/kg as a 10% solution by stomach tube to five cats and three dogs daily for 14 d, Chenoweth et al. (1941) found no evidence of toxicity. Urine was examined daily for protein, blood, casts, and sugar. Gross examination of lungs, heart, liver, kidneys, gastrointestinal tract, bladder, ureters, and spleen as well as histological examination of lungs, liver, and kidneys were performed.

Chenoweth et al. (1941) administered oral doses of glucono delta-lactone (80-170 mg/kg/d) for 3-6 d to five healthy human subjects. There was no sign of renal injury as judged by examining urine for protein, casts, blood cells, pus cells, and sugar.

Male and female rats (20/group) received 0 or 10,000 ppm (about 500 mg/kg) gluconolactone delta-lactone in the diet for 26 wk. There were no reported adverse effects and no histopathological findings (Harper and Gaunt, 1962).

Sixteen persons (seven with urologic conditions) received doses of 5 g gluconolactone delta-lactone every 2 h up to total doses of 15-25 g daily for 2 d usually followed by a 2-day control period, then 10-25 g doses every 2 h up to total doses of 20-50 g for an additional day (Gold and Civin, 1939). No consistent changes in the pH of the urine were detectable. However, diarrhea was observed in 11 of the 16 patients. No other adverse effects were reported.

Long-term toxicity

A 29-mo feeding study by van Logten et al. (1972) designed to study effects of nitrite reaction products in cured meats, incorporated several groups of rats fed diets containing gluconolactone delta-lactone (GDL). Six groups of weanling Wistar rats, each of 30 males and 30 females, were fed the following diets: (1) control; (2) 40% meat; (3) 40% meat treated with 0.5% NaNO₂; (4) 40% meat treated with 0.5% NaNO₂ and 1% GDL; (5) 40% meat treated with 0.02% NaNO₂ and 1% GDL; or (6) 40% meat treated with 1% GDL. Measurements included: body weights, feed consumption, hematology, serology, sulfobromophthalein retention, serum glutamic-pyruvic transaminase, serum alkaline phosphatase, aniline hydroxylase, aminopyrine demethylase, glucose-6-phosphatase, alpha-fetoprotein, and DNA content of liver cell nuclei. Histopathological examinations were also conducted. Rats receiving gluconolactone delta-lactone added to meat in the diet did not differ from controls with respect to growth, feed intake, mortality, and histopathology. Mean body weights were higher and feed intake greater for all animals on the meat diets. After 18 mo, the mortality was generally greater among animals receiving the meat diets. Growth was inhibited in the rats that received the 0.5% NaNO₂ with or without gluconolactone delta-lactone. Nitrite added to a meat diet resulted in a decrease in erythro-
cytes. All evaluations of liver function failed to demonstrate any adverse effect of NaNO2 with or without glucono delta-lactone or of glucono delta-lactone alone. The incidence of tumors was not greater in the rats receiving the meat diets.

Special studies

The mutagenic effects of glucono delta-lactone were assessed in the following microbial assays with and without activation: Saccharomyces cerevisiae, Salmonella typhimurium strains TA-1535, TA-1537, TA-1538 (Litton Bionetics, Inc., 1974). Glucono delta-lactone was not mutagenic in any assay.

The administration of glucono delta-lactone to pregnant mice, rats, hamsters, and rabbits failed to affect nidation, maternal survival, or fetal survival (Food and Drug Research Laboratories, Inc., 1973). Pregnant albino CD-1 mice (six groups of 25) received 0, 6.95, 32.5, 150, and 695 mg glucono delta-lactone/kg body wt by oral intubation from day 6 to day 15 of gestation. Pregnant Wistar rats (six groups of 22-25) received 0, 5.94, 27.6, 128, and 594 mg glucono delta-lactone/kg body wt by oral intubation from day 6 to day 15 of gestation. Pregnant hamsters (six groups of 25) received 0, 5.6, 121, and 560 mg glucono delta-lactone/kg body wt by oral intubation from day 6 to day 15 of gestation. Pregnant Dutch-belted rabbits (six groups of 10) received 0, 7.80, 36.2, 168.5, and 780 mg glucono delta-lactone/kg body wt by oral intubation from day 6 to day 18 of gestation.
V. OPINION

Phosphorylated derivatives of glucono delta-lactone and gluconic acid, the hydrolysis product of glucono delta-lactone, are intermediates in glucose metabolism in the pentose phosphate shunt. Glucono delta-lactone is used as an acidulant in leavening agents, as a buffer or neutralizing agent, and as a color-fixing accelerator in meat-curing processes. In aqueous solution, it forms an equilibrium mixture with gluconic acid and its delta- and gamma-lactones. The per capita daily consumption of glucono delta-lactone resulting from its use as an added ingredient is believed to be less than 1 mg.

Glucono delta-lactone is absorbed from the gastrointestinal tract, metabolized by normal metabolic pathways, and, depending on the amount ingested, some may be excreted in the urine. Acute and short-term toxicity studies suggest a very low order of toxicity. Long-term animal studies at multiple feeding levels have not been reported; however, one long-term feeding study in rats suggests no adverse effects. Glucono delta-lactone was nonmutagenic in several microbial assays and nonteratogenic in tests with mice, rats, hamsters, and rabbits.

On the basis of the available data, the Select Committee concludes that:

There is no evidence in the available information on glucono delta-lactone that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future.
VI. REFERENCES CITED

Beebe, A.J. 1963. Food and Drug Administration, Washington, DC. Memorandum, dated August 14, to the Director, Atlanta District, Bureau of Field Administration, Food and Drug Administration, Atlanta.


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August 12, 1981

Date

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Select Committee on GRAS Substances