EVALUATION OF THE HEALTH ASPECTS OF
POTASSIUM GLUCONATE AS A FOOD INGREDIENT
Supplemental Review and Evaluation

1980

Prepared for

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

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Life Sciences Research Office
Federation of American Societies for Experimental Biology
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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 (SCOGS), 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.

The Federation and the FDA have agreed that when additional information and data become available subsequent to completion of an evaluation report, the FDA may request review and evaluation of the supplemental information and data by the Select Committee. Based upon the reevaluation of all available data, the Select Committee will prepare a supplemental report. This particular report on potassium gluconate is a supplement to a report prepared on gluconate salts by the Select Committee (SCOGS, 1978).
The supplemental reports are also approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee. Upon completion of these review procedures, the supplemental 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.

[Signature]

Kenneth D. Fisher, Ph.D., Director
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I. INTRODUCTION

This report concerns the health aspects of using potassium gluconate as a food ingredient. It has been based partly on the information contained in scientific literature reviews (monographs) furnished by FDA (Bond and Feinman, 1974; Dailey, 1978), which summarize 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 the combined knowledge and experience of members of the Select Committee and the LSRO staff.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarketing 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, 1980) [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 evaluated this substance 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. The Committee anticipates that its conclusions will be reviewed as new information becomes available.

In this supplemental report, the Select Committee on GRAS Substances has evaluated information on potassium gluconate made available recently (Dailey, 1978) and has reevaluated the information contained in its previous report on certain gluconate salts (SCOGS, 1978). The conclusion reached in this supplemental report is intended for the use of the FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act.
II. BACKGROUND INFORMATION

Potassium gluconate [HOCH₂-(CHOH)₄-COOK] is the potassium salt of gluconic acid. It consists of yellowish-white crystals that decompose at 180°C; it is readily soluble in water and insoluble in alcohol, ether and chloroform (The Merck Index, 1976). Gluconic acid is a normal product of glucose oxidation in mammals (White et al., 1973). It forms easily soluble salts with a number of cations (sodium, potassium, iron, magnesium, manganese, copper, zinc). Such salts provide a practical means of introducing these cations into the body for therapeutic or nutritional reasons (Sawyer, 1964). For example, potassium gluconate is used therapeutically as an electrolyte replenisher in the treatment of hypokalemia (National Formulary XIV, 1975).

In the food industry, potassium gluconate is considered "unpublished GRAS" as a nutrient (Subcommittee on Review of the GRAS List--Phase II, 1972; Food and Drug Administration, 1973; Wulfsberg, 1966).

Specifications for food grade potassium gluconate are not included in the Food Chemicals Codex (National Research Council, 1972) but the requirements for the pharmaceutical grade are the following: should contain not less than 97.0% C₆H₁₁KO₇, dry basis; not more than 0.002% heavy metals; less than 3% loss on drying; and should exhibit only infrared maxima at the same wavelengths as reference standard potassium gluconate (National Formulary XIV, 1975).

Potassium gluconate and the gluconates of calcium, sodium, magnesium, zinc, copper, manganese, and iron have been evaluated previously (SCOGS 1975, 1978, 1979a, 1979b, 1980). The Committee found no evidence in the available information that demonstrated or suggested grounds to suspect hazard from the use of these compounds at current levels as food ingredients. However, almost no data on potassium gluconate itself were found at that time. The Select Committee's opinion and conclusion were based largely on reasoned judgment that this salt of gluconic acid must be non-hazardous, inasmuch as gluconic acid is a normal metabolic product and potassium is a dietary essential. Since that time a new search for relevant information concerning potassium gluconate has been made (Dailey, 1978). This information, together with that previously available, is reevaluated in the present supplemental report.
III. CONSUMER EXPOSURE DATA

In the reports of its surveys of food manufacturers in 1970 and 1975, the National Research Council (NRC) (Subcommittee on Review of the GRAS List--Phase II, 1972; Committee on GRAS List Survey--Phase III, 1978) noted potassium gluconate was first used in food in the United States in 1943. The NRC did not request manufacturers to estimate current usage levels of poundage of potassium gluconate used in food annually; nor did any of the industry respondents volunteer information on the nature and extent of use of potassium gluconate, suggesting that this salt is not now being added to foods. If it should be added, however, it is likely that it would be used as an alternative to sodium gluconate which was used at the time of the survey at weighted mean levels of 0.17% in processed fruits, juices, and drinks, and 0.07% in non-alcoholic beverages. The quantity of sodium gluconate used for these purposes in 1970 was 38,000 kg, amounting to about 0.5 mg per capita daily. If all of this were replaced by potassium gluconate, the per capita daily intake of potassium from this source could be about 0.08 mg, and of gluconate, about 0.42 mg. In light of this information, the Select Committee believes that the daily per capita consumption of potassium gluconate, due to that added to foods, is considerably less than 0.5 mg (less than 8 μg/kg body weight) in an adult.

For comparative purposes the following data are noteworthy. Potassium is widely distributed in foods. In healthy adults, efficient homeostatic mechanisms allow for a wide range of intake which has been estimated to be 2.3–3.9 g (Randall, 1980) or 1.95–5.9 g daily (National Research Council, 1980). The endogenous daily production of gluconate is some 25–30 g (SCOGS, 1978).
IV. BIOLOGICAL STUDIES

Absorption and metabolism

After oral administration, potassium gluconate is absorbed readily from the intestine. In rats receiving 2.1 meq/kg (490 mg/kg) of potassium gluconate orally, potassium concentration in the blood serum peaked in 3 h and had returned to normal levels after 9 h; potassium concentration in the urine peaked at 6 h and returned to initial level after 10 h. The concentration of potassium in the serum and urine reached higher levels per unit time after feeding potassium gluconate than after feeding an equivalent dose of potassium chloride, suggesting that potassium from the gluconate salt is more readily absorbed than from the chloride salt (Tomizawa, 1975). Orally administered gluconates of calcium (Lieberman, 1930), sodium (Lindsay, 1958), and magnesium (Di Mattei and Butturini, 1934) have been shown to be more effective as cationic supplements than other salts of these elements.

Gluconate is a normal product of glucose oxidation (White, et al., 1973; Stetten and Topper, 1955). After phosphorylation of glucose, catabolism can proceed through the glycolytic cycle or by the direct, oxidative phosphogluconate pathway. Activity of the latter is minimal in muscle tissue and much greater in liver, adipose tissue, adrenal cortex, thyroid, leucocytes, testis, and the lactating mammary gland; in some of these tissues, as much as 30% of the glucose may be metabolized through this pathway.

A significant portion (60-85%) of parenterally administered gluconate is excreted unchanged in the urine. However, gluconate is readily catabolized (Wang et al., 1962) or utilized for glucose synthesis, mainly from CO₂ derived from carbon 1 and from glucogenic compounds derived from carbons 2 through 6 of the gluconate (Stetten and Stetten, 1950; Stetten and Topper, 1953). Renal excretion of gluconate appears to be by tubular secretion (Herken et al., 1975).

Acute and chronic toxicity

No acute oral or parenteral toxicity data on potassium gluconate were found by the Select Committee. However, studies of compounds containing either the potassium or gluconate ions indicate that the acute toxicity of such compounds is of low order. The minimal lethal intravenous dose of sodium gluconate has been reported as 7.6-8.7 g/kg body weight in rabbits (Gajatto, 1939). The minimum lethal dose of potassium chloride in rats is 100 mg/kg intravenously and 2.43 g/kg orally (Loeser and Konwiser, 1929; Ulrich and Shternov, 1929).
The Select Committee has been unable to find reports of chronic feeding studies of potassium gluconate in laboratory animals. However, indirect evidence is provided in the work of Greenstein et al. (1957) who made quantitative nutritional studies with water-soluble, chemically-defined diets. Their basal diet, containing the equivalent of 23 g of potassium gluconate per kg, was supplemented with various amino acid mixtures and fed (daily intake of potassium gluconate about 2.3 g/kg body weight assuming an average animal weight of 100 g) to Sprague-Dawley rats for 60-100 days without evidence of adverse effects. In studies of the effect of several substances on metabolic rate, gluconic acid fed to rats at a level of about 400 mg/kg had no effect on metabolic rate and no other adverse effects were noted (Berta and Győri, 1942).

Circumferential small-bowel ulcers have been associated with the irritant effects of potassium chloride used in potassium replenishment therapy (Morgenstern et al., 1965). Potassium gluconate appears to be less irritating in this respect. It has been tested by fixing tablets within the ileum or distal jejunum of dogs so that absorption would occur within a limited segment of the intestine (Boley et al., 1967). The dogs were sacrificed after 5-7 days and all tissues surrounding the tablet site were examined microscopically. No remarkable gross changes were seen at any of the sites where potassium gluconate was implanted. Minimal superficial hemorrhage was noted in 40% of the sites where tablets containing 7.0 g potassium gluconate were used; 10% of the sites with 3.5 g tablets; none of the sites with 2.3 g tablets. While histologic changes were minimal, the authors suggested that high concentration of potassium ions (which would not be expected in food use) was not completely without physiologic and anatomic effect on the bowel. Pathological changes were less with potassium gluconate tablets than with potassium chloride tablets at the same dose level.

Potassium gluconate is used clinically to replenish potassium in patients experiencing hypokalemia. The usual adult dose is about 9 g in equal portions after meals and at bedtime (Physicians' Desk Reference, 1978). Francois (1962) has reported on the evaluation of potassium gluconate given daily to 10 patients in oral doses of about 6-12 g. The authors reported the product to be remarkably well tolerated at such levels with no digestive or metabolic disturbances. Goenen and Coche (1969) also found that potassium gluconate is better tolerated than potassium chloride since 50 of 100 patients experienced digestive disturbances after receiving the chloride compared with 3 in 100 receiving an equivalent dose of the gluconate.
Other related studies

The Select Committee has been unable to find reports of the testing of potassium gluconate for teratogenicity or mutagenicity. However, tests with other gluconates and other salts of potassium suggest that neither the potassium nor gluconate ions would be active in either respect. Neither sodium gluconate nor zinc gluconate was found to exhibit mutagenic activity in microbial tests using Saccharomyces cerevisiae and Salmonella typhimurium (Litton Bionetics, 1975a and 1977). Zinc gluconate, tested in the developing chick embryo, was found to display no teratogenicity when injected into the air cell or yolk of unincubated eggs (dose range 10–200 mg/kg) or after 96 h of incubation (dose range 2.5–100 mg/kg) (Verrett, 1978). Potassium chloride was found to be non-mutagenic in in vitro microbial assays employing S. cerevisiae, strain D4, and S. typhimurium, strains TA-1535, -1537, and -1538, with or without activation using preparations of liver, lung, and testis from ICR mice, Sprague-Dawley rats, or the primate, Macaca mulatta (Litton Bionetics, 1975b). Teratologic examination of potassium chloride in mice and rats showed that the administration of up to 235 mg/kg body weight to pregnant mice, and up to 310 mg/kg body weight to pregnant rats for 10 consecutive days, had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ significantly from the number occurring spontaneously in the sham-treated controls (Food and Drug Research Laboratories, 1975).
V. OPINION

Potassium, the cation of potassium gluconate, is an essential nutrient. It is widely distributed in foods and 2-6 g are consumed by adults daily from all sources. Gluconic acid, the anion of potassium gluconate, is a normal metabolic product of glucose metabolism, 25-30 g being produced daily. For these reasons, and because potassium gluconate is widely used therapeutically as a source of potassium in cases of hypokalemia, conventional toxicological studies of potassium gluconate have not been regarded as necessary, explaining the lack of direct animal data on the compound. Orally administered gluconate is absorbed rapidly; a major part is excreted in the urine and the remainder is metabolized.

There is no evidence that potassium gluconate is now being added to processed foods. If it were to be used, it is likely that it would be added in place of sodium gluconate in such products as processed fruits, juices and drinks, where the quantity used amounts to some 0.5 mg/capita/day.

Based on the foregoing, and the information considered in its previous report on gluconates, the Select Committee concludes that:

There is no evidence in the available information on potassium gluconate that demonstrates or suggests reasonable grounds to suspect a hazard to the public should it be used at levels now used for sodium gluconate, or that might reasonably be expected in the future.
VI. REFERENCES CITED


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September 3, 1980

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