EVALUATION OF THE HEALTH ASPECTS OF SUCCINIC ACID

AS A FOOD INGREDIENT

1975

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
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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 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
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I. INTRODUCTION

This report concerns the health aspects of using succinic acid as a food ingredient. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (I), 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, announcement was made in the Federal Register of August 29, 1975 (40 FR 39917 and 39918) 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 succinic acid as a food ingredient. The Select Committee received no requests for such a hearing on succinic acid.

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 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

*The document (PB-223 860/8) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
public health. While the Select 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 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 reconducted, 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 succinic 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

Succinic acid, 1,4-butanedioic acid (HOOCCH₂CH₂COOH), is a natural constituent of fresh meat, cheese, and such vegetables as asparagus, beets, broccoli, rhubarb, and sauerkraut, all of which have distinct flavors that may, in part, be related to the succinic acid content. When applied to growing plants, succinic acid increases rate of growth and yield (2). Succinic acid is found in the mitochondria of animal and plant cells where it functions as an intermediary metabolite in the citric acid cycle (1).

Succinic acid can be isolated as colorless or white, odorless, monoclinic crystals that elicit a strong acid taste. It is moderately soluble in cold water and in alcohol. Pure aqueous solutions have been described as slightly bitter. Food grade succinic acid should assay not less than 99 percent of C₄H₆O₄ and contain not more than 3 ppm of arsenic and 10 ppm of heavy metals (as lead) (3). Succinic acid can be manufactured by the catalytic hydrogenation of maleic or fumaric acid, and has also been produced by aqueous alkali or acid hydrolysis of succinonitrile (2).

As a food ingredient succinic acid is used as an acidulant; and because it combines readily with proteins, is used to modify plasticity. The Code of Federal Regulations classifies succinic acid among the substances Generally Recognized as Safe (GRAS) as a miscellaneous and/or general purpose food additive (4). It was first used as a food ingredient in the United States in 1962 (5).
A report of a subcommittee of the National Research Council (NRC) (5) has provided information on the usual use levels of succinic acid in various categories of foods. The subcommittee surveyed manufacturers by questionnaire concerning the addition of succinic acid to their processed products, grouped by categories. Based on the information supplied by those manufacturers who reported adding succinic acid to at least one food product in a food category, a weighted mean was calculated for the usual percentage addition to foods in that category. For a given category, the mean of the usage levels reported by a manufacturer was multiplied (weighted) by the ratio of total pounds used by that manufacturer in all categories to the total pounds (all categories) reported by manufacturers that reported use in the category. The weighted means for the percentage of succinic acid added to the two food categories in which it is used, were 0.01 percent in meat products and 0.08 percent in condiments, relishes, and salt substitutes. It is to be noted that these weighted means do not express the highest percentage of succinic acid added by any manufacturer; they do not indicate which specific foods in a category contain added succinic acid; and they do not necessarily coincide with the levels used by any one industry in its products in the food categories listed.

III. CONSUMER EXPOSURE DATA

The NRC subcommittee has also provided (Table I) information on the possible average daily intakes of succinic acid by age groups (5). Since food consumption data were not requested in the subcommittee survey, intake estimates were derived by utilizing Market Research Corporation, Chicago, Illinois, data on mean frequency of eating foods by category, U.S. Department of Agriculture data on mean portion size, and by assuming that all food products within the two food categories to which succinic acid is added, contained succinic acid at the levels indicated in Section II of this report, namely, 0.01 percent in meat products and 0.08 percent in condiments, relishes, and salt substitutes. Because of factors detailed in the NRC subcommittee's report, they stated that their estimated average total dietary intakes (Table I) are high; they are likely to be much higher than would be the intakes achieved through consumption of a diet consisting totally of processed foods to which succinic acid has been added at maximum levels.
### TABLE I

Possible Average Daily Intake of Added Succinic Acid by Age Group (5)

<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>0.1</td>
<td>0.02</td>
</tr>
<tr>
<td>6-11 mo</td>
<td>1.9</td>
<td>0.24</td>
</tr>
<tr>
<td>12-23 mo</td>
<td>4.2</td>
<td>0.38</td>
</tr>
<tr>
<td>2-65+ yr</td>
<td>12.2</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Calculated by the Select Committee, based on an average weight of 60 kg for an adult (6) 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 (7).

The Select Committee agrees that these intake estimates must be higher than actual and could be achieved by only a small fraction of the population. An opportunity for making an alternative calculation is provided in other data contained in the NRC subcommittee report (5). Respondents to the subcommittee's survey indicated that they used 383 pounds (174 kg) of succinic acid in food products in 1970. The NRC subcommittee estimated that this amount represented about 60 percent of the total used by the food industry in that year. By recalculating the poundage to 100 percent and assuming a population of 205 million, an intake of less than 0.01 mg per person per day is obtained. The Select Committee believes that an intake of added succinic acid of less than 0.01 mg per day is more reasonable than the figures in Table I for individuals over 2 years of age, and that intakes by younger individuals are likely to be even less than 0.01 mg per day.

### IV. BIOLOGICAL STUDIES

**Metabolism and excretion**

Succinic acid is one of the dicarboxylic acids involved in the citric acid cycle. As one of the intermediates in this cycle, it may participate in the net synthesis of glucose and other sugars and fatty acids in animal tissue (8).
Succinic acid fed to phlorizindinized dogs was converted to glucose. As the dose was increased, a smaller percentage was excreted in the urine as glucose, but antiketogenic and nitrogen sparing activity indicated its conversion to glucose before being oxidized (9). Stoehr (10) fed 0.15 g of neutralized succinic acid to fasted young rats and noted a marked increase in liver glycogen four hours after feeding. When given by stomach tube to fasting rats with fatty livers, succinic acid and equivalent amounts of glucose were equally effective in reducing ketosis. The antiketogenic action of succinic acid in the intact organism was considered to be simply a result of its conversion to glucose (11). Ingestion of 10 to 50 g per day of free succinic acid by diabetic patients caused no antiketogenic activity when measured by the ketonuria, while in the normal fasting individual it was as antiketogenic as an equivalent amount of glucose (11).

In studies of the bioavailability of energy from various aliphatic chemicals added to the diets of experimental animals, Yoshida et al. (12) found that succinic acid at the 5 percent dietary level was well utilized by rats. Sodium succinate produced a 22 percent hypoglycemic response when injected into rabbits (13). Urinary citric acid from fully grown rats was measured after oral administration of the sodium salts of various organic acids given in the ratio of 60 mg sodium per 100 g body weight. After sodium succinate was given (estimated to be about 150 mg succinate per 100 g of body weight), the 24 hour urine sample contained 4.18 mg of citric acid per ml as compared with 0.44 mg of citric acid per ml in rats given sodium carbonate, and 0.16 mg of citric acid per ml in control animals (14).

**Acute toxicity**

The minimum lethal dose of succinic acid injected subcutaneously into frogs was 2 g per kg body weight (15). Rabbits tolerated 0.54 g of succinic acid injected intravenously as an 0.5 N solution, or 1.63 g of 0.25 N solution per kg body weight (16). Rose (17) gave rabbits 4.0 g (about 2 g per kg of body weight) of neutralized succinic acid subcutaneously as the sodium salt and concluded that the acid is not nephrotoxic in rabbits because of the rapid oxidation of succinic acid within the organism. Intraperitoneal injection of 4 g per kg body weight of succinic acid in Long-Evans rats was the maximum tolerated dose, which was defined as the dose at which 10 percent of the test animals died in 24 hours (18). The oral LD$_{50}$ of a mixture of succinic acid (63.3 percent) and magnesium phosphate (36.7 percent) in mice was 4562 mg per kg body weight (19).

**Short-term studies**

Albino rats, seven days old, were injected subcutaneously with 0.5 mg of succinic acid in sesame oil, and daily thereafter with increasing doses until they were receiving 2.0 mg per day at four weeks of age (estimated to
be approximately 20 mg succinic acid per kg body weight per day); this dosage was continued until the rats were 60 days old. Control animals received similar doses of sesame oil only. All the rats were weighed and measured weekly, and the times of hair appearance, tooth eruption, eye opening, and vaginal opening were recorded. There were no significant differences between the treated and the control animals except for a possible tendency toward delayed opening of the vagina in the test rats (57.2 days) compared with the controls (49.4 days) (20).

In another series of experiments 0.05 ml of a 1:1000 solution of succinic acid (0.05 mg) was injected into the air sacs of fertile hen eggs on the tenth day of incubation. Control eggs were injected with phosphate buffer solution. No significant differences in weight and rate of development between the chicks of treated and control eggs were noted at hatching, and surviving chicks from treated eggs all developed to maturity without incident (20).

Single intraperitoneal injections of succinic acid, 4 g per kg body weight, had a sedative effect on the central nervous system and significantly increased brain dopamine in male Long-Evans rats. The mode of action was not determined (18). Sodium succinate (1 g per kg body weight) administered to rabbits (route not reported), shortened the duration of drug-induced sleep. The author suggested that succinic acid influences the duration of drug-induced sleep by increasing the excretion rate of the soporific (21).

**Long-term studies**

No long-term toxicity tests with succinic acid have been reported.

**Reproduction**

Possible estrogenic properties of succinic acid were investigated in two-month-old ovariectomized rats. Daily subcutaneous injections of 5 mg of succinic acid (estimated to be approximately 31 mg per kg body weight per day) for 3 weeks did not change the typical diestrous vaginal smears (20).

**Teratogenicity**

Injection of 7.5 mg of sodium succinate hexahydrate into the yolk sacs of fertile hen eggs at 96 hours of incubation produced no discernible toxic or teratogenic effects in the embryos (22).
Effect on teratogens

When the yolk sacs of chick embryos were injected simultaneously with sodium succinate hexahydrate and certain teratogens, the succinate decreased the teratogenicity of 3-acetylpyridine, 6-aminonicotinamide, and sulfanilamide, but potentiated the teratogenicity of insulin (22). The investigators suggested that the teratogens interfered with mitochondrial energy production and that high energy intermediates such as succinate, fed into the respiratory chain of the mitochondria and functioning as energy sources, can decrease the incidence and modify the degree of expression of malformations produced by specific teratogens.

Drug interaction

The absorption of orally administered ferrous sulfate in human subjects increased in direct proportion to supplemental doses (30 to 100 mg) of succinic acid given orally and intravenously (23). Eighty-one subjects participated, 13 of whom were healthy volunteers, and 68 healthy, non-anemic persons who had served as blood donors for various periods of time but had received no iron supplementation. The investigators measured the fraction of absorbed iron utilized in hemoglobin formation and suggested that succinic acid increases intestinal mucosal cell metabolism which influenced the transfer of iron across the cell membranes. On the other hand, when succinic acid was administered orally or intravenously to normal, adult subjects in single doses of 15 or 110 mg and in daily doses given for 10 days, no increase in the whole-body absorption of iron from oral doses of ferrous succinate was observed (24, 25).

An incubated mixture of 100 mg of sodium succinate and 2 units of insulin, injected into rabbits' legs, decreased the hypoglycemic effect of insulin; however, simultaneous but separate injections of the two compounds produced little or no change in insulin activity compared with insulin alone (13).

No studies on possible carcinogenic or mutagenic effects of succinic acid were found by the Select Committee.

V. OPINION

Succinic acid occurs widely as a natural constituent of the plants and animals which are commonly used for human food. As one of the intermediary metabolites in the citric acid cycle, it may participate in the net synthesis of glucose and other sugars and fatty acids normally present in
plant and animal tissue. At the level succinic acid occurs naturally in foods, there is no evidence that it is hazardous to man or animals. Moreover, experimental animals tolerate succinic acid in amounts equivalent to several g per kg of body weight. By contrast, a reasonable average daily intake of succinic acid added to foods is estimated to be less than 0.01 mg per day, a dosage that is orders of magnitude less than that required to elicit toxic signs in experimental animals.

There have been few scientific studies designed to explore possible untoward effects of succinic acid. However, the normal role of succinic acid as an intermediary metabolite in living organisms including man, is persuasive in favor of its safety.

Based on these considerations, the Select Committee concludes that:

There is no evidence in the available information on succinic acid 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


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Report submitted by:

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