EVALUATION OF THE HEALTH ASPECTS OF
DEXTRANS AS FOOD INGREDIENTS

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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
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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.

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I. INTRODUCTION

This report concerns the health aspects of using dextrans 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 1974.* 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 dextrans as food ingredients. The Select Committee received no requests for such a hearing on dextrans.

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 health 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

*The document (PB-234 889/4) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
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 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 dextrans 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

Dextrans are high molecular weight polysaccharides composed almost exclusively of the monomeric unit, α-D-glucopyranose, linked mainly through carbon atoms 1 and 6 of adjacent units. The chemical structure of a dextran is determined primarily by the bacterial strain that produces it. Dextrans are synthesized from sucrose by the nonpathogenic bacteria *Leuconostoc mesenteroides* and *L. dextranicum* and from dextrins derived from starch by *Acetobacter capsulatum* and *A. viscosum*. Dextrans also are produced from sucrose by *Streptococcus* and *Lactobacillus* species (2). *S. mutans* and *S. sanguis* have been isolated from dental plaques and demonstrated to be dextran producers (3-5). A cariogenic strain of *L. acidophilus* was shown to produce an extracellular polysaccharide that was antigenically similar to dextrans (6). A strain of *L. casei*, isolated from human gingival crevice, synthesized an extracellular dextran (7).

Although the predominant linkage between glucopyranose units in all dextrans is 1,6, linkages through carbon atoms 1 and 4, 1 and 3, and/or 1 and 2 also occur (8-12). The proportion of the different type linkages is determined mainly by the bacterial strain. Jeanes et al. (8) reported a wide variation in chemical structure and physical properties of dextrans produced by 96 strains of bacteria.

Dextrans are found in sugar mills and refineries when sucrose-containing solutions become contaminated with dextran-producing bacteria that commonly occur in these facilities (13). Dextrans also develop naturally in frost-damaged sugar cane and in cut cane if processing is delayed (14).
They have been detected by serological tests in many samples of refined crystalline sucrose (15, 16), maple syrup and sauerkraut juice (17), and honey (18). Water-insoluble dextran flavored with fruit syrups constitutes the commercially produced Philippine dessert nata (2). Higuchi et al. (19) showed that dextran was the principal polysaccharide in dental plaque and comprised about 3.7 percent by weight of dry plaque.

Dextran produced commercially in the United States, Canada, Sweden and elsewhere is synthesized from sucrose by Leuconostoc mesenteroides strain NRRL B-512(F) (20). This dextran has a molecular weight in the range of 30 to 90 million; partial depolymerization and fractionation results in a series of lower molecular weight products which are marketed principally for pharmaceutical and industrial non-food uses. The NRRL B-512(F) dextran has 95 percent of the glucopyranose units linked through carbons 1 or 1 and 6; 5 percent carry branches predominantly one or two glucose units long attached at carbon 3 positions (9).

The major pharmaceutical use for dextran in the U.S. is as a blood plasma substitute. For this purpose dextrans of weight-average molecular weight 75,000 ± 25,000 have proved effective and much of the biological testing has been done with such dextrans. A preparation of molecular weight 40,000 ± 20,000 has been used in surgical procedures to reduce aggregation of erythrocytes and increase fluidity of the blood (2).

Dextrans of average molecular weight below 100,000 are generally recognized as safe (GRAS) as miscellaneous and/or general purpose food additives (21).

III. CONSUMER EXPOSURE DATA

A number of applications for dextran in food has been described including its use in syrups and candies to increase moisture retention, improve body and inhibit crystallization of the sugar; as a coating film to protect foods such as meats, dried fruits and cheese against dehydration in storage; as a stabilizing or bodying agent in soft drinks and in a variety of other uses (22). However, as far as the Select Committee is aware, the only current food use for dextran is as a beverage base in combination with liquid glucose and a flavoring agent (23). Distribution of this product appears to be limited. No use of dextran in food was reported in the 1970 survey (24) conducted by a subcommittee of the National Research Council (NRC). A low background exposure to dextran arises from dextran consumed as an impurity in sucrose. Exposure may also be contributed by dextran synthesized in the oral cavity by bacteria associated with dental plaque formation.
Absorption, metabolism, excretion

Dextran is digested and absorbed from the gastrointestinal tract of animals and man. Bloom and Wilkelmi (25) reported that oral administration of dextran (3 g per kg body weight) to 24-hour-fasted male rats resulted in a 40 percent increase in blood sugar 1 hour after feeding and 19 percent at 4 hours. Increase in level of blood sugar also was observed in four 12-hour-fasted human subjects at one-half hour (23 percent increase) and 2 hours (18 percent increase) after ingestion of 100 or 200 ml of 20 percent dextran (0.33 to 0.67 g per kg body weight). They found that dextran fed to human subjects was not recovered in the stools. In the rat it was shown that increase in blood sugar was accompanied by an approximate fourteenfold increase in liver glycogen as determined 4 hours after feeding. The rapid increase in blood sugar indicated that the breakdown of dextran was not solely due to action of dextran-degrading bacteria, which have been isolated from human feces (26, 27), but that an enzyme in the intestinal mucosa also was involved (28).

Parkinson (29) administered by stomach tube 500 mg (1.8 g per kg body weight) dextran, molecular weight 75,000, to 24-hour-fasted male Sprague-Dawley rats. Glycogen determinations on liver excised 4 hours later showed a sixfold greater concentration in rats that received dextran compared to that of control animals receiving distilled water. Homogenates of intestinal mucosa which were prepared from rats fasted 24 hours showed dextranase activity. Several tissues of rats, rabbits, dogs and cattle were shown to contain dextran-splitting enzymes (30). Activity decreased in the following order: spleen and liver, kidney, lung and brain, and muscle; no dextranase activity was detected in blood. The only products of dextranase action were glucose and residual dextran; hence the enzyme was classified as an $\alpha$-glucosidase. Ammon (31) found that the spleen, liver and kidneys of humans also contained a dextranase. More pertinent to the digestion of orally ingested dextran was the finding of dextranase activity in extracts of small-intestinal mucosa of the rat, guinea pig, rabbit, pig, cow, dog and man (25, 32, 33). Rosenfeld (34) recently reported that $\alpha$-glucosidases from human and animal tissues hydrolyzed dextrans containing 1,6- and 1,3- linkages almost completely but only partially hydrolyzed dextrans containing 1,2- linkages.

Hellman (35) studied the metabolism of intravenously infused carbon-14 labeled dextran in man and found that within 10 days after infusion, 64 percent of the radioactivity was eliminated in the urine and 26 percent in expired carbon dioxide; about 2 percent appeared in the feces. These findings indicate metabolism of dextran in man after intravenous infusion.
Terry et al. (36) infused five dogs intravenously with 0.78 to 1.30 g per kg body weight of carbon-14 labeled dextrans, molecular weight 66,000 and 86,000, and followed the distribution of radioactivity in the urine, expired air and blood at intervals over a period of 3 to 13 days. The animals were sacrificed and radioactivity in various tissues was determined. After 72 hours, 55.6 to 76.0 percent of the radioactivity appeared in the urine largely as dextran, and 4.6 to 9.0 percent in the expired air. At sacrifice after 3, 4, 5, 12 and 13 days a total of 8.7, 14.5, 10.9, 5.1 and 3.5 percent, respectively, of the infused radioactivity was found in liver, muscle, skin and hair, and other tissues. Since [14C] carbon dioxide production continued after circulating plasma levels were reduced to negligible levels, the authors concluded that dextran was metabolized after deposition in the tissues.

Gray and Highland (37) determined the metabolic half-life of carbon-14 labeled dextran, molecular weight 86,000, from the residual radioactivity in the whole carcass of adult white mice 1 to 5 weeks after infusion (0.5 to 0.6 g per kg body weight) in the tail vein. Metabolic half-life was 6.1 days; residual radioactivity at 5 weeks after infusion was 0.2 percent of the total activity infused. Radioactivity measurements were made on lipid, carbohydrate and protein fractions extracted from the carcasses of animals sacrificed 1 to 25 days after infusion. Radioactivity in the protein fraction increased rapidly in the first 2 days after infusion and then decreased rapidly for the next few days. After the fifth day the level was low and decreased very slowly. Activity in the carbohydrate fraction was highest on the first day, probably reflecting the presence of residual dextran. As in the case of the protein fraction, radioactivity in the carbohydrate fraction fell sharply. Uptake of carbon-14 in carcass lipids was considerably slower, reaching a peak about the fifth day and then declining slowly. The data were interpreted as indicating that dextran is broken down by the animal, incorporated into the carbon pool and converted into substances normally found in the animal.

Evidence for intestinal absorption of polymeric dextran was presented by Bienengräber and coworkers (38) who reported the presence of fluorescent-labeled dextran in the epithelial cells of intestinal villi of 36-hour-fasted female Wistar rats sacrificed 5 to 120 minutes after drinking 0.5 percent solutions of dextran, 80,000 molecular weight, labeled with dansyl chloride.

**Acute toxicity**

Irikura et al. (39) reported that clinical dextran (molecular weight 70,000) was not toxic at a dose of 12 g per kg for mice and 3 g per kg for rats when administered orally in isotonic solution containing 6 percent dextran and 5 percent glucose. Injected in the tail vein of mice at a rate
of 1 ml of 6 percent solution per minute, the LD₅₀ values for dextran were 12.1 and 13.0 g per kg for females and males, respectively. Corresponding LD₅₀ values for rats were 6.9 and 8.2 g per kg when injected at the rate of 3 ml per minute. For intravenously infused dextran, Long et al. (40) reported an LD₅₀ in dogs of about 12 g per kg. Gelin and Ingelman (41) found that intravenously administered doses (15 percent solution) up to 42 g per kg could be given to mice without causing death.

**Short-term studies**

Booth et al. (42) included dextran in a study on the physiological effects of the oral ingestion of microbial polysaccharides by rats. In subacute toxicity tests, NRRL B-512(F) dextran was fed at a 15 percent level for 62 days to weanling white albino rats. Dextran replaced part of the corn starch in a basal ration consisting of corn meal, crude casein, linseed oil meal, alfalfa meal, cod liver oil, bone ash, sodium chloride and corn starch. Weight gain and feed efficiency did not differ significantly from that of the control group. No adverse physiological effects were reported. Caloric availability and digestibility of dextran were determined by feeding dextran as a supplement to a commercial rat chow at restricted caloric levels. At 16.4 percent level in the diet, digestibility of a high-molecular-weight dextran was 86 percent and that of a low-molecular-weight dextran was 90 percent; digestibility of another dextran fed at a 7.4 percent level was 78 percent. Weight gain on dextran diets was comparable to that on the basal diet supplemented with glucose at similar levels, indicating good utilization of dextran.

**Long-term studies**

The Select Committee is not aware of any reports on long-term animal feeding studies of dextran.

**Special studies**

An extensive study (43) of the carcinogenicity of dextrans and other macromolecular substances administered to mice and rats for up to 2 years and to rabbits up to 4 years, reported the appearance of sarcomas in the tissues in which the substances were retained and stored. The dextrans differed in degree of branching and in molecular weight and were administered in single and multiple doses through the subcutaneous and intraperitoneal routes to mice (10 g per kg body weight) and rats (5 g per kg) and intravenously to rabbits (8.8 to 16.8 g per kg total dose). A branched dextran, 89,400 molecular weight, was most carcinogenic as measured by the percentage of treated animals affected, compared either to dextrans more or less highly branched or to homologous dextrans of similar degree of
branching but higher or lower in molecular weight. Control animals in these experiments exhibited some cancers but at considerably lower incidence and did not show the different developmental and precancerous changes found in the affected treated animals. Because of the parenteral administration of the dextrans, this information was of questionable value to the Select Committee in considering the food use of dextran. The following test with iron-dextran was viewed similarly. Weekly intramuscular injection of an iron-dextran complex into male adult albino rats, each dose equivalent to about 70 mg iron as ferric hydroxide per kg body weight, over a period of 11 to 16 months resulted in tumors at the site of injection in 16 of 23 rats. However, rats given weekly injections of dextran, 110 mg per kg, or normal saline solution did not develop tumors (44).

Intravenous infusion of clinical dextran in humans lowered cholesterol and plasma lipid levels; initial levels were regained 3 to 7 weeks after treatment (45,46). Oral administration of 60 ml of 6 percent dextran solution for 30 days (1.8 g per kg total dose) resulted in a reduction in cholesterol and other serum lipid levels equivalent to that obtained by the intravenous administration of dextran (47). No effect of orally ingested dextran on serum lipids was reported in another study (46).

Allergic reactions have been reported in humans receiving intravenous infusions of clinical dextran for the first time. Incidence of reactions appeared to be related to chemical structure in a comparison of two dextrans; the one having the greater proportion of non-1,6-linkages caused a greater incidence of untoward reactions (48). The more highly branched dextran also gave a higher incidence of positive skin tests and precipitated antibody nitrogen from preinfusion sera of a greater proportion of individuals. Although subcutaneous injection of dextran elicited antibody formation in humans (49-51), intravenous infusion of clinical dextran apparently did not (48). Occurrence of preinfusion antibodies was attributed to exposure to dextran as an impurity in commercial sucrose or to dextran produced by organisms in the gastrointestinal tract. Alternatively, the skin sensitivity and precipitable antibodies were suggested to result from cross reaction with antibacterial antibodies arising from previous infections (48,52,53). Dextrans cross react with types II, XII and XX rabbit antipneumococcal sera (52-54). Extent of reaction was associated with the chemical structure of the dextran (12). Dextrans also cross react with antisera to Salmonella typhi, other members of this Salmonella group (55,56) and to Streptococcus, group H (57).

Allergic or anaphylactic reactions have been reported in less than 1 percent of the patients who received infusions of clinical dextran. Unfavorable reactions were reported in less than 1 percent of 1,500 patients who received Swedish clinical dextran prior to 1948 (58) and 10 among 13,434 patients in the period 1955 to 1958 (59); 15 of 1,647 patients who
received a British dextran solution prior to 1952 exhibited urticarial, allergic or anaphylactoid reactions (60); and 11 allergic reactions were reported among 2,657 administrations of Czechoslovakian-produced clinical dextrans over the period 1960-1968 (61). Although the occurrence of allergic reactions to dextran on intravenous infusion is well documented, the significance of this information to ingestion of dextran as a food is questionable.

No studies were found on the mutagenicity, teratogenicity or fetotoxicity of dextrans.

V. OPINION

Dextrans are polysaccharides composed of $\alpha$-D-glucopyranose units and are commercially prepared by the action of bacterial enzymes on sucrose. They occur naturally in small amounts in such foods as refined crystalline sugar, maple syrup, sauerkraut juice and honey and also as a component of dental plaque.

No use of dextran in food was reported in the 1970 survey of food processors conducted by a NRC subcommittee and the Select Committee concludes that any undisclosed use was probably small. More recently, however, one company has marketed a beverage product containing dextran. Current distribution and use of this product also appear to be small.

Oral ingestion studies in animals and man have shown that dextran is broken down by intestinal enzymes and is absorbed from the gastrointestinal tract. Intravenously administered dextran also is metabolized in animals and man. Weight gain of rats fed diets containing 15 percent dextran in short-term tests was comparable to that on a glucose supplemented diet indicating good utilization of dextran as an energy source. No adverse physiological effects were noted in these tests nor were any reported in acute toxicity tests.

The absence of evidence of harm in the limited biological tests that have been conducted and the extensive use of dextran as a blood volume expander without untoward effects, except for reaction of an allergic type in a low percentage of patients, support the opinion of the Select Committee that the use of dextran in food at present levels poses no problem. However, there is no long history of use of dextran as an ingredient of food products. Should the level of use be increased, particularly as a beverage product in which dextran is a major component, the existing scientific data are insufficient for judgment as to possible health hazards.
In light of the foregoing, the Select Committee concludes that:

There is no evidence in the available information on dextran that demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine without additional data, whether a significant increase in consumption would constitute a dietary hazard.
VI. REFERENCES CITED


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