EVALUATION OF THE HEALTH ASPECTS OF CORN SUGAR (DEXTROSE),
CORN SYRUP, AND INVERT SUGAR AS FOOD INGREDIENTS

1976

Prepared for

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

Contract No. FDA 223-75-2004
EVALUATION OF THE HEALTH ASPECTS OF CORN SUGAR (DEXTROSE),
CORN SYRUP, AND INVERT SUGAR AS FOOD INGREDIENTS

1976

Prepared for

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

Contract No. FDA 223-75-2004

Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
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
FASEB
<table>
<thead>
<tr>
<th>CONTENTS</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>5</td>
</tr>
<tr>
<td>IV. Biological studies</td>
<td>9</td>
</tr>
<tr>
<td>V. Opinion</td>
<td>15</td>
</tr>
<tr>
<td>VI. References cited</td>
<td>18</td>
</tr>
<tr>
<td>VII. Scientists contributing to this report</td>
<td>25</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

This report concerns the health aspects of using corn sugar (dextrose), corn syrup, and invert sugar as food ingredients. It has been based partly on the information contained in two scientific literature reviews (monographs) furnished by FDA (1), which summarize 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 on January 22, 1976 (41 FR 3332 to 3334), 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 corn sugar (dextrose), corn syrup, and invert sugar as food ingredients. Two requests were received. The Select Committee held a hearing on May 24, 1976. Those who requested opportunity to present data, information and views are identified at the end of this report. The material presented at the hearing has been considered by the Select Committee in reaching its final conclusions.

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 Code of Federal Regulations 21 CFR 121.1, revised April 1, 1976, 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.

*These documents (PB-223 853/3 and PB-241 963/8) are available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
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 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 corn sugar (dextrose), corn syrup, and invert sugar 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

Corn sugar (dextrose), corn syrup (glucose syrup), and invert sugar are direct and indirect food ingredients. Corn sugar, corn syrup and invert sugar are cited as generally recognized as safe (GRAS) in the Code of Federal Regulations as substances that may migrate to food from paper and paperboard products used in food packaging (2). The Code of Federal Regulations also indicates that dextrose, corn syrup and invert sugar are permitted as ingredients of various food products (3). The Food and Drug Administration regards corn syrup and dextrose as among those substances "presumed to be GRAS but unpublished," Exhibit 9, Appendix A, part 2 in reference 4.

Corn sugar, commonly referred to as dextrose, is crystalline α-D-glucose. Nearly all crystalline dextrose is produced in the U.S. by the hydrolysis of corn starch. After partial hydrolysis with acid or the enzyme α-amylase, conversion is completed by the enzyme glucoamylase which produces only glucose by progressive hydrolysis from the non-reducing ends of the starch molecules. The starch source of dextrose is not specified in the GRAS listing. Dextrose may be crystallized as the monohydrate or in the anhydrous form (5). Identity standards for dextrose monohydrate specify that the total solids content should not be less than 90 percent and the reducing sugar content, expressed as D-glucose, should be not less
than 99.5 percent calculated on a dry basis; the sulfated ash content should be not more than 0.25 percent, dry basis; and the sulfur dioxide content should be not more than 20 mg per kg (6). The same standards also state that the name of the food is "dextrose monohydrate" or "dextrose."

Identity standards for anhydrous dextrose state that it conforms to the specifications of dextrose monohydrate except that the total solids content is not less than 98.0 percent (6).

Corn syrup is a class of products obtained by the partial hydrolysis of corn starch. Syrups from edible starches, including corn starch, are more generally referred to as glucose syrups. In addition to α-D-glucose, corn syrup contains various proportions of di-, tri-, and higher saccharides which are composed of anhydroglucose units joined primarily through α-1,4' glucosidic linkages. New syrup products recently described are the high-fructose and dextrose-levulose (fructose) syrups produced by enzymatic isomerization of glucose in high-conversion starch hydrolyzates (7) or in solutions of dextrose (8), respectively. These syrups are similar in composition to invert syrups from sucrose in their content of dextrose and fructose.

In the production of corn syrups, depolymerization of starch may be accomplished by acid hydrolysis, preliminary acid hydrolysis followed by enzymatic hydrolysis or hydrolysis by a combination of enzymes. When the desired extent of conversion has been reached, the acid hydrolyzates are neutralized and enzymes are inactivated. The resulting solution is clarified by filtration or centrifugation, concentrated by evaporation, decolorized with carbon and, for some products, demineralized by ion-exchange. The distribution of products obtained depends upon the conversion agents and the extent of hydrolysis. Generally, however, the higher the conversion, the greater the proportion of mono-, di- and low molecular weight saccharides formed (9, 10). Identity standards for glucose syrup specify that total solids content be not less than 70.0 percent and the reducing sugar content (dextrose equivalent) expressed as D-glucose be not less than 20.0 percent calculated on a dry basis. The standards also specify that the sulfated ash content be not more than 1.0 percent, dry basis, and the sulfur dioxide content not more than 40 mg per kg (6).

Identity standards also have been promulgated for dried glucose syrup (6). This product must conform to the specifications for glucose syrup except that total solids shall not be less than 90.0 percent when the reducing sugar content expressed as dextrose equivalent is not less than 88.0 percent, dry basis, also, total solids shall not be less than 93.0 percent when the reducing sugar content expressed as D-glucose is less than 88.0 percent, dry basis.
In addition to glucose, maltose, higher oligosaccharides and dextrins present in corn syrups, the relative proportions depending on the conversion degree and agents, other reaction products may be present, particularly in the case of high-conversion acid-hydrolyzed syrups. Glucose may recombine in the presence of acid catalysts to form disaccharides other than maltose which is derived directly from starch; the glucose may also be degraded in the presence of acid to form hydroxymethylfurfural and levulinic acid (11). Both reactions are favored by high temperatures. Ough (12) separated the following disaccharides from an acid-converted corn syrup having a reducing sugar content of 60 percent expressed as dextrose: laminaribose (α-D-1, 3′ glucosidic linkage), 0.2 percent; nigerose (α-D-1, 3′), 0.8 percent; maltose (α-D-1, 4′), 15.5 percent; cellobiose (β-D-1, 4′), 0.4 percent; kojibiose (α-D-1, 2′), 0.2 percent; β, β-trehalose (β-D, β-D-1, 1′), 0.2 percent; isomaltose (α-D-1, 6′), 1.6 percent; and gentiobiose (β-D-1, 6′), 0.3 to 2.3 percent. Kerr (11) estimated that under the range of conditions employed in the commercial hydrolysis of starch by acid, less than 1 percent of glucose reacts to form hydroxymethylfurfural, levulinic acid and related products. Under the conditions of temperature and acidity employed in enzymic hydrolysis of starch, recombination and decomposition occur to much less extent (13). Corn syrups, dextrose equivalent above 42, now are produced generally by an acid-enzyme or enzyme-enzyme process.

Not included in the identity standards for glucose syrup but manufactured by similar processes are the maltodextrins which are defined by the corn wet milling industry as "purified concentrated solutions (or dry products made therefrom) of nutritive saccharides obtained from starch and having a D.E. (dextrose equivalent) of less than 20" (10). The maltodextrins thus differ from glucose syrup in that the extent of hydrolysis of starch is less. Because of their close relation to glucose syrup the Select Committee considers them as glucose syrup for the purpose of this report.

Invert sugar is a mixture of two monosaccharides, glucose and fructose, which results from the hydrolysis of sucrose. Invert sugar is marketed as a component of invert syrups; these syrups also contain sucrose, the proportion depending on the extent of conversion. Invert syrups are considered to be invert sugar in this evaluation. Solids in "total" invert syrups contain 6 percent sucrose whereas those in "medium" invert syrups contain 39 percent sucrose (8). Invert syrup solids also contain 3 percent polysaccharides and less than 0.5 percent of the monosaccharide D-psicose (an epimer of fructose). The principal high-fructose syrup currently sold in the United States is produced by the enzymatic isomerization of starch hydrolyzates, about 95 dextrose equivalent, and contains about the same proportions of dextrose and fructose as "total" invert syrups from sucrose on a dry solids basis. It also contains the di- and higher saccharides that were present in the starch hydrolyzates from which they were derived and less than 0.3
percent D-psicose (7, 10). Dextrose-levulose syrup produced by the enzymatic isomerization of dextrose solutions contains, in addition to dextrose and levulose, less than 1 percent polysaccharides and less than 0.3 percent D-psicose (8).

III. CONSUMER EXPOSURE DATA

Corn syrup was first used in food in the United States in 1895, dextrose ten years later in 1905 (4). According to Agricultural Statistics (14), 1970 annual per capita consumption as food of corn syrup and dextrose estimated from disappearance data was 15.8 and 5.0 pounds (7.2 and 2.3 kg), respectively, which correspond to 19.6 and 6.2 g per day. This was an increase of 57 and 28 percent, respectively, over the consumption of these products in 1960. It should be pointed out that disappearance data include the quantities of corn sweeteners used in malt beverages and yeast-leavened baked goods in which the sweetener is fermented to carbon dioxide or other products and thus does not contribute to dietary intake. A survey of food manufacturers by a National Research Council Subcommittee (4) indicated 1970 per capita consumption of 10.1 and 5.1 g per day for corn syrup and dextrose, respectively, based on poundage data adjusted to take into account the subcommittee's estimate that about 60 percent of total poundage used was included in their survey. Comparable data are not available for invert sugar, nor are data available concerning the corn syrup or invert sugar content of paper and paperboard products used in food packaging.

The National Research Council Subcommittee survey (4) provided information on the level of addition of corn syrup and dextrose to foods in several food categories as given in Table I. The NRC Subcommittee surveyed manufacturers by questionnaire concerning the usual and maximal levels of addition of these products to foods. Based on 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 percentage addition of each substance to food products in the categories. For a given category, the mean of the usage levels reported by a manufacturer was weighted by the ratio of the pounds used by that manufacturer in all food categories to the pounds (all categories) used by those manufacturers that reported use in the category. Only the weighted mean usual level of addition is reported in Table I.
TABLE I

Level of Addition of Corn Syrup and Dextrose to Foods by Food Category (4)

<table>
<thead>
<tr>
<th>Food category</th>
<th>Corn syrup Weighted mean percent</th>
<th>Dextrose Weighted mean percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>4.87</td>
<td>3.14</td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td>11.34</td>
<td>8.43</td>
</tr>
<tr>
<td>Grain products such as pastas or rice dishes</td>
<td>15.15</td>
<td>2.24</td>
</tr>
<tr>
<td>Fats and oils</td>
<td>6.70</td>
<td>1.69</td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>2.74</td>
<td>3.86</td>
</tr>
<tr>
<td>Cheese</td>
<td>1.22</td>
<td>1.26</td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td>9.91</td>
<td>0.26</td>
</tr>
<tr>
<td>Processed fruits, juices and drinks</td>
<td>5.39</td>
<td>3.86</td>
</tr>
<tr>
<td>Fruit ices, water ices</td>
<td>2.27</td>
<td>0.57</td>
</tr>
<tr>
<td>Meat products</td>
<td>1.22</td>
<td>0.60</td>
</tr>
<tr>
<td>Poultry products</td>
<td></td>
<td>1.30</td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td>4.60</td>
<td>12.48</td>
</tr>
<tr>
<td>Condiments, relishes salt substitutes</td>
<td>9.68</td>
<td>4.98</td>
</tr>
<tr>
<td>Soft candy</td>
<td>27.61</td>
<td>49.36</td>
</tr>
<tr>
<td>Sugar, confections</td>
<td>25.16</td>
<td>21.01</td>
</tr>
<tr>
<td>Jams, jellies, sweet spreads</td>
<td>7.36</td>
<td>5.22</td>
</tr>
<tr>
<td>Sweet sauces, toppings syrups</td>
<td>45.48</td>
<td>0.36</td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>6.90</td>
<td>6.57</td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Snack foods</td>
<td>26.00</td>
<td>0.33</td>
</tr>
<tr>
<td>Beverages, non-alcoholic</td>
<td>2.24</td>
<td>3.07</td>
</tr>
<tr>
<td>Beverages, alcoholic</td>
<td>0.90</td>
<td>1.00</td>
</tr>
<tr>
<td>Nuts, nut products</td>
<td>8.72</td>
<td>11.25</td>
</tr>
<tr>
<td>Reconstituted vegetable proteins</td>
<td></td>
<td>3.43</td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>9.53</td>
<td>3.86</td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>33.19</td>
<td>5.05</td>
</tr>
<tr>
<td>Hard candy</td>
<td>24.74</td>
<td></td>
</tr>
<tr>
<td>Chewing gum</td>
<td>9.02</td>
<td>12.88</td>
</tr>
<tr>
<td>Seasonings and flavors</td>
<td>14.27</td>
<td>2.34</td>
</tr>
<tr>
<td>Baby formulas</td>
<td>6.25</td>
<td>4.07</td>
</tr>
<tr>
<td>Baby processed fruit</td>
<td></td>
<td>2.35</td>
</tr>
<tr>
<td>Baby puddings</td>
<td></td>
<td>3.40</td>
</tr>
</tbody>
</table>

Blanks in the table mean that the substance is not added to the foods indicated. Level of addition of corn syrup and dextrose 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 text, also Section X and Exhibit 50 of reference 4.
The NRC subcommittee estimated possible average daily intakes (Table II) from Market Research Corporation of America data on 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 foods within a category contain the substance at the level shown in Table I. Such an assumption is likely to lead to overestimates of intake. The NRC subcommittee has recognized that in most cases its calculations of possible intakes are overstated, often by considerable margins.* Because of factors detailed in Section XI of the subcommittee's report (4), it was stated that the average estimated 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.

**TABLE II**

<table>
<thead>
<tr>
<th>Substance</th>
<th>0-5 mo g/kg</th>
<th>6-11 mo g/kg</th>
<th>12-23 mo g/kg</th>
<th>2-65+yrs g/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn syrup</td>
<td>22</td>
<td>4</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Dextrose</td>
<td>17</td>
<td>3</td>
<td>19</td>
<td>2</td>
</tr>
</tbody>
</table>

Calculated intake, mg/kg body weight, was based on an average weight of 60 kg for an adult (15) and the following estimated weights of infants by age groups: 0-5 mo, 5 kg; 6-11 mo, 8 kg; and 12-23 mo, 11 kg (16).

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (4). 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 on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
The estimates of possible average intakes in Table II, particularly for dextrose, exceed by severalfold the per capita intakes based on the total quantity of corn syrup and dextrose consumed annually as food as reported by Agricultural Statistics. The average intakes of corn syrup and dextrose by infants given in Table II appear to be particularly overstated. About 10 percent of U.S. infants, 0 to 5 months, are fed formulas based on protein from soy isolate and nearly all the remainder receive milk-based formulas or are breast-fed (17). The usual concentration of 6.25 percent for corn syrup concentration in infant formulas (Table I) could apply only to milk-free formulas because at least 50 percent of carbohydrate in other formulas is necessarily supplied in the form of lactose as a component of milk solids. Actually, the added carbohydrate in most milk-based formulas at present is lactose but increasing use of corn syrup solids may be anticipated in the future. Dextrose is not included as an ingredient of formulas marketed as concentrated liquids because of the Maillard reaction that occurs when dextrose-containing formulas are heat-treated in the manufacturing process. A small percentage of powdered formulas contain dextrose but these are products designed for managing infants with specific abnormalities such as disaccharide intolerance.

No information was provided in the NRC survey on the consumption of invert sugar or the proportion of corn syrup used that was high-fructose corn syrup. However, Friend and Marston (18) estimated that the total daily per capita consumption of fructose from all foods as the monosaccharide increased from 4 g in 1971 to 6 g in 1974 based on domestic food disappearance data. This may be compared with the per capita daily consumption of 66 g fructose provided by the 1974 sucrose consumption of 126 g. The 2 g per capita increase was attributed chiefly to the development and use of high-fructose corn syrup. This increased consumption of high-fructose corn syrup is consistent with an estimated production of 0.92 billion pounds, dry solids basis, in 1974 (19) and 1 billion pounds projected for 1975 (20), comprising about one-fifth of the corn syrup marketed. High-fructose corn syrup, on a dry substance basis, has the same sweetness as sucrose and can be used in food products on an equivalent sweetness basis except in those products where a dry sweetener is required (7). Forecasts of up to 30 percent penetration of sucrose markets by 1980 to 1985 have been made (19,20). More recently, however, Kolodny (21) has estimated that high-fructose corn syrup would comprise about 14 percent of the total sweetener market in 1980 as compared to about 6 percent in 1975. All corn sweeteners were projected to increase from about 24 percent of the sweetener market in 1975 to about 30 percent in 1980.
IV. BIOLOGICAL STUDIES

Absorption and metabolism

Maltose and higher saccharides present in corn syrup are not absorbed as such but are converted to glucose in the digestive process. Glucose and fructose are primarily absorbed by the mucosa of the small intestine although the sugars can also be absorbed from the colon. Glucose is absorbed primarily by an active transport mechanism and to a very limited extent by diffusion. Its absorption is relatively independent of the amount ingested. Although the mechanism of fructose absorption has not yet been completely elucidated it appears to occur by facilitated or carrier-mediated diffusion (22). Absorption of fructose into the blood was found to be 50 to 80 percent greater when ingested as sucrose by fasted men and women than when ingested as an equivalent amount of a mixture of glucose and fructose (23). Ockerman and Lundburg (24), studying human jejunum at operation, found that up to 70 percent of absorbed fructose was converted to glucose as measured in mesenteric venous blood, whereas White and Landau (25) found a maximum conversion of 26 percent as measured by the incorporation of carbon from labeled fructose into glucose and glycogen.

The major pathways of glucose and fructose metabolism are well known. Glucose from the plasma is metabolized mainly by glycogen formation, anaerobic glycolysis via the Krebs cycle and conversion to fat (26, 27). Absorbed fructose is largely converted to glucose in the liver and is metabolized as glucose. Glucose excretion in the urine occurs when rapid absorption provides an excessive blood sugar concentration and in disease conditions such as diabetes mellitus (28). Fecal excretion occurs only in the case of malabsorption or sudden excessive ingestion (29).

Saunders and Isselbacher (30) found that transport of the neutral amino acids alanine and glycine was inhibited in rat intestinal slices by the presence of fructose; in intestinal slices from rats fed fructose 2 to 3 months only alanine transport was inhibited. Comparable tests with glucose showed no effect.

Acute toxicity

Acute toxicity of dextrose in chicks has been determined by Kopfler and Wilkinson (31). Chicks 18 to 20 hours old and weighing from 40 to 45 g were given a 40 percent dextrose solution orally at a rate of 0.2 g of dextrose per hour (about 5 g per kg body weight per hour). When this excessive amount was administered the chicks survived about 13 hours. Mortality was attributed to critical tissue water losses caused by the high osmotic pressure of the solution. However, the same workers found that when an
8 percent dextrose solution was administered at the rate of 0.1 g of dextrose per 30 minutes, no deaths occurred. Only minor water depletion in the skin and skeletal muscle was observed.

In experiments on dextrose and fructose conducted by Orcel et al. (32), the LD₅₀ dose for rats, administered intravenously, was found to be about 10 to 12 g per kg body weight. Lethal doses produced changes in the liver, particularly in the periportal hepatocytes. An LD₅₀ dose of glucose increased serum transaminase activity, sulfobromophthalein retention and serum concentrations of aldolase, pyruvic acid and lactic acid. The no-effect level on transaminase activity was about 2.5 g per kg. An LD₅₀ dose of fructose caused only moderate increase in transaminase activity and less pronounced sulfobromophthalein retention.

Studies carried out in the rabbit by Evans (33) showed that the intravenous administration of up to 30 g of dextrose in rabbits weighing 2 kg failed to produce pathological effects.

The LD₅₀ for maltodextrin administered orally was reported to be greater than 34.6 g per kg body weight in Charles River rats weighing 142 to 190 g. In an eye irritation test on non-sterilized maltodextrin, transient irritation was noted within one hour after instillation of 100 mg of test material in the eye of albino rabbits. Ocular tissues of all animals returned to normal within 24 to 72 hours (34).

**Short-term studies**

Bachman et al. (35) fed rats for 10 weeks on equicaloric diets containing 68 percent of either dextrose or fructose, equivalent to about 50 g per kg of body weight. Weight gain and feed efficiency were found to be the same for the two sugars. The average total glycogen and nitrogen content of the whole body was the same for the two groups. Total body fat content was significantly greater in the dextrose-fed rats. The fructose-treated rats exhibited increased hydration of body tissue and significant hypertrophy of the liver. No serious untoward effects were observed.

In another study (36), adult male rats were fed diets containing about 81 percent carbohydrate (about 40 g per kg of body weight) given as dextrose (anhydrous), sucrose, fructose and spray-dried liquid glucose for 26 weeks. The liquid glucose was identified as aqueous preparation of partially hydrolyzed starch with a dextrose equivalent of 42.5 and containing 76.5 percent carbohydrate. The content of dextrose, 18.7 percent; maltose, 13.9 percent; maltotriose, 11.2 percent; maltotetrose, 9.8 percent; and higher oligosaccharides, 44.4 percent, in the dry product indicate the product was prepared by acid hydrolysis of starch and was similar in
composition to a 42.5 dextrose equivalent commercial glucose syrup. The animals receiving dextrose exhibited lower weight gain than did control rats receiving a standard laboratory diet containing 50 percent carbohydrate, mainly as starch. However, weight gain of the animals receiving the glucose syrup was not significantly different from that of the control animals. Compared to controls, the plasma cholesterol concentrations were significantly increased in rats by fructose and sucrose and, to a lesser degree, dextrose, but not by glucose syrup. Hearts, kidneys, and livers were significantly heavier in animals receiving fructose, but organ weights of those given glucose syrup did not vary significantly from the controls. Sucrose also caused an increase in heart and liver weight, but dextrose caused an increase only in heart weight. Sucrose and fructose, but not dextrose or glucose syrup, increased liver dry weight and fat content. Liver protein content was significantly lower in animals on the test diets than those on the control diet; reductions were greatest for dextrose and sucrose as the carbohydrate source.

A study carried out by Röhm et al. (37) showed that 20 percent dextrose solutions (about 70 g per kg of body weight) given exclusively for eight days to male Wistar rats, 217 g average weight, resulted in the formation of ulcers in the upper end of the stomach. After two days of dextrose feeding, single ulcers were present in this part of the stomach, increasing in size and number until the twelfth day. No ulcers were found in the small intestine. The ulcers healed rapidly when the rats were placed on a normal diet. The authors ascribed the development of the stomach ulcers to gastric juice that was not required for digestion and was therefore directed to the stomach wall. They pointed out that the upper part of the rat stomach is not similar to that found in humans and concluded that extrapolation to man should be made only with extreme caution.

Becker and Terrill (38) carried out a 39-day feeding study with 9-week-old pigs maintained on semi-purified diets containing 50 percent of various carbohydrates, including dextrose (about 23 g per kg body weight). They found that dextrose produced satisfactory weight gain and feed efficiency.

Allen et al. (39) fed mature baboons diets containing 74 percent available carbohydrates as sucrose for 26 weeks; these animals had higher total serum lipid and serum lipoprotein than did baboons maintained on a diet containing 74 percent available carbohydrate as liquid glucose (glucose syrup, dextrose equivalent 42.5) or animals fed a diet containing 47 percent of available carbohydrate as starch with 4.5 percent sucrose and 4.5 percent liquid glucose. The combined weight of abdominal and epididymal fat was significantly greater in the animals fed sucrose than in those fed the other diets.
Andrews and Cook (40) fed glucose, sucrose or lactose to 30 premature infants weighing between 1,418 and 2,077 g. The infants were initially fed dextrose at 4 to 6 hours of age at 0.5 g per kg body weight. Subsequently, the carbohydrates were fed as a part of a soy isolate-based formula supplying 4.15 g of the carbohydrate per kg body weight per day and were gradually increased to 11.5 to 12.2 g per kg per day by the fifth day of life in eight equal feedings. The infants were maintained on these regimens until they reached a weight of five pounds. No statistically significant difference was established among the groups for percent weight loss, days to regain birth weight, weekly weight gains, or caloric efficiency; no adverse clinical findings were observed.

Special studies

Studies by Uebelin (41) showed that a single dose of 1 g (5.5 g per kg body weight) of dextrose given to 180 g rats by stomach tube caused an intense lymphopenia which was attributed to the secretion of ACTH. Treatment of weanling rats with 1 g of dextrose orally per day (14 g per kg body weight) for 14 days was found to produce atrophy of the thymus. Simultaneous administration of adenine suppressed both responses.

Peters and Strother (42) and Strother et al. (43) reported that high intakes of dextrose increased the duration of sleep induced by barbiturates and decreased the metabolism of barbiturates. In these experiments, mice were given 30 to 35 percent dextrose solution to drink (ad lib) for two days.

In order to examine the carcinogenicity of dextrose, Cappellato (44) subjected 5- to 6-month-old rats to daily subcutaneous injections of 2 to 4 cc of a 25 percent dextrose solution (2.5 to 5 g per kg body weight). Control animals were injected with physiological saline. Subcutaneous fusiform and polymorphous cellular sarcomata were observed in two of 55 animals. A third animal had a sarcoma in the abdominal cavity after 299 injections. Hueper (45) carried out a study in mice and rats in which 0.5 to 2.0 ml, respectively, of 25 percent dextrose (about 5 g per kg) were injected two or three times a week for periods up to two years. No tumors were found at the site of injection and no indication of any untoward effects was observed. The data on carcinogenicity, therefore, are unconfirmed, and the relevance of subcutaneous injections to ingestion is questionable.

There are conflicting reports on the allergenicity of corn sugar and corn syrup. Ingestion of corn sugar and corn syrup and intravenous injections of corn sugar (dextrose) were reported by Randolph et al. (46, 47) to result in the production of allergic symptoms in some individuals highly sensitive to corn. From "blindfold" ingestion studies of 25 patients with
histories suggestive of corn allergy, Loveless (48) reported a few cases of reaction to large feedings of the starches of corn, tapioca and arrowroot, but no case of susceptibility to corn syrup or corn sugar. Bernton (49) also reported failure to demonstrate sensitivity to corn syrup in ingestion tests of an individual sensitive to corn meal and corn starch. In a review of the possible allergenicity of table syrups, Fisher and Carr (50) concluded that there were no studies demonstrating that chemically pure glucose, sucrose or fructose can function as a hapten or allergen in individuals known to be sensitive to corn, sugar beets or sugar cane.

Yudkin (51, 52) has suggested that increased consumption of sucrose, as compared to starch and other complex carbohydrates, is an important factor in the etiology of coronary heart disease and diabetes. Since sucrose and starch differ chemically in their constituent monosaccharide units, much of the research on dietary sucrose has focused on the metabolic effects of fructose. High levels of fructose in the diets of animals and humans have been found to increase the plasma triglyceride concentration. Nikkila and Ojala (53) compared triglyceride plasma levels in white, male rats, 250 to 300 g, on a commercial rat chow diet supplemented with glucose or fructose given as a 10 percent solution in the drinking water. Average daily intake of sugars was 8 g glucose and 6 g fructose (about 30 g and 20 g per kg body weight, respectively). After 2 and 4 weeks blood samples were collected from 2 hour fasted animals; glucose-supplemented diets caused a 60 percent increase in plasma triglycerides whereas fructose supplementation resulted in a 160 percent increase. In a similar experiment with both male and female rats, Bar-On and Stein (54) found fructose-supplemented diets raised the serum triglyceride about 90 to 250 percent after 6 and 19 days on the supplemented diet. Serum triglycerides of rats on the glucose-supplemented diet were about equal to or lower than those of control animals. Fructose supplementation in drinking water of guinea pigs for 6 days had no effect on the serum triglyceride level as compared to those receiving glucose. The high activity of glucose-6-phosphatase in the guinea pig intestine, resulting in the conversion of fructose to glucose before absorption, was proposed to explain this finding. Both rats and guinea pigs were fasted 16 hours before sacrifice.

Macdonald (55) fed fat-free diets providing 7 g carbohydrate per kg body weight and 50 g calcium caseinate daily for 5 days to men and to pre- and postmenopausal women. Carbohydrate was starch, or 40 dextrose: 60 starch, or 40 fructose: 60 starch, or 40 fructose: 60 dextrose. Fasting serum lipid level determined on the last two days was increased most by the fructose-dextrose diet (61 and 120 percent in men and postmenopausal women, respectively) and least by the dextrose-starch diet (-19 and 27 percent, respectively). Serum lipids in premenopausal women were decreased when
fructose was included in the diet. In a recent review paper, Macdonald (56) pointed out that the effect of dietary fructose on the fasting level of serum triglyceride is modified by the sex of the consumer, the amount and type of fat accompanying the fructose, the type of protein in the diet and the frequency of intake. Ahrens (57) has pointed out the practice of determining serum lipid levels after an overnight fast tends to overestimate the effect of carbohydrates, since people on a high carbohydrate diet show a peak in serum triglyceride levels just before breakfast. In contrast, people on a liberal fat diet show a minimum serum triglyceride level at this time and a peak concentration some 4 hours later.

Carbohydrates, particularly sugars, have been implicated as a dietary cariogenic factor by epidemiological studies and animal feeding experiments. Worldwide, there appears to have been a positive correlation between caries incidence and the introduction of refined sugar and flour (58). But dental caries can and do occur in populations that have never used sugar or any other processed foodstuff (59). The most common factors associated with caries development in a study of over 80 patients with rampant dental caries were a history of frequent or excessive eating of sweets during and between meals, extensive bacterial plaque formation and lower pH levels in plaques than in mucous membranes or saliva (60). Studies of eating habits of preschool and school children have indicated a correlation between the number of caries and the number of confections or quantity of sugar consumed between meals (61, 62) but not between dental caries experience and total sugar consumed (62). A 5-year study of 436 adult patients in Vipeholm Hospital under controlled dietary regimens showed that in evaluating the effect of sugar intake, not only the quantity of sugar consumed must be considered, but also the form in which it is served and whether it is consumed at or between meals. For example, it was found that patients placed on a diet with reduced sugar content showed an increase in caries activity when they received a small portion of the reduced amount of sugar between meals (63).

Cariogenic activities of sugars, starches and foods have been compared in experiments with rats and hamsters. Reports differ on the relative cariogenicity of sucrose and glucose. Studies on rats (60, 64-66) and hamsters (66) showed that sucrose promoted greater caries activity than glucose. Other investigators have found that in rats the relative activity of these two sugars was not significantly different (67, 68); depended on the rat strain, glucose being equally cariogenic in the rice rat but less in the Harvard caries-susceptible strain (69); or depended on both the microflora of the mouth and the rat strain (70). Cariogenic activity of fructose in animals appears to be similar to that of glucose (64-66). Fructose was as cariogenic as sucrose in humans when compared by the intra-oral cariogenicity test in which a slab of enamel is placed in an oral prosthetic device and worn within the
mouth (71). Although emphasis in most studies of cariogenicity has been on the simple sugars as food additives, there is evidence that complex carbohydrates and natural foods promote caries activity as components of animal diets. Sprague-Dawley rats fed powdered diets containing 60 percent pre-gelatinized potato starch developed over twice the number of carious areas at 30 days as did rats fed a comparable diet containing sucrose but this ratio was reduced to about one-half after 60 days on the diets (72). Stephan (60) fed basal noncariogenic and cariogenic diets, supplemented with 53 test foods and beverages, to a caries-susceptible strain of Osborne-Mendel rats. Supplements were offered ad lib between two daily feedings. Twenty-seven foods were significantly cariogenic on the noncariogenic basal diet and most of them, all containing fermentable sugars, significantly increased caries on the cariogenic diets. Included among these foods were figs, apples, bananas, grapes, raisins, dates, honey, and rye bread as well as cookies, mints, chocolate, dextrose and sucrose. Sucrose was the most cariogenic.

No studies on the mutagenicity or teratogenicity of dextrose have come to the attention of the Select Committee.

V. OPINION

Corn sugar, commonly referred to as dextrose, is crystalline α-D-glucose. Glucose is widely distributed in nature both in the free state and in various combined forms, including starch and sucrose. Glucose-yielding carbohydrates constitute one of the main sources of energy in the typical North American diet. Fructose, produced along with glucose in the hydrolysis of sucrose to invert sugar and by isomerization of dextrose, also is a significant dietary calorie source. The absorption and metabolism of these sugars are well established. Biological studies have shown that these substances are devoid of toxic effects at dosage levels well in excess of those that exist in the American diet and, accordingly, at levels that are orders of magnitude higher than those which might occur from the migration of these substances from paper and paperboard products.

Glucose syrup, also called corn syrup when made by the hydrolysis of corn starch, contains in addition to glucose, maltose, and higher saccharides in proportions that depend on the degree of hydrolysis of the starch. The higher conversion syrups may also contain small amounts of disaccharides formed by the recombination of glucose through glucosidic linkages not present in starch. Animal feeding studies have shown that glucose syrups are readily digested and metabolized and have given no evidence of toxic effects.
Fructose-dextrose mixtures have been observed to have hyperlipemic effects when fed at high levels in fat-free diets to adult males and postmenopausal women. There is no evidence, however, that the levels of invert sugar and high-fructose corn syrup in the average diet cause significant elevations in blood lipids and it is unlikely that the consumption of fructose or glucose, ingested as monosaccharides, has a role in coronary heart disease.

Although glucose and fructose as well as sucrose have been demonstrated to be cariogenic in animal experiments, epidemiological studies of dietary habits and controlled diets in institutional feeding indicate that the cariogenicity of sucrose and other foods is affected by several factors and not necessarily by the total amount consumed. These factors include the frequency of eating, duration of exposure, and the form and physical properties of the food in which the sugar is ingested. Between-meal eating has been demonstrated to be significantly correlated with frequency and severity of caries in both children and adults. Thus, protection is facilitated by limitation of the frequency of consumption of sugar and sugared foods.

Consumption of dextrose and corn syrup has increased markedly in recent years and represented about 21 percent of the sweetener market in 1974 as compared to about 15 percent in 1970. A major part of the increase resulted from the introduction of high-fructose corn syrup produced by the enzymatic isomerization of dextrose in starch hydrolyzates. Level of fructose as the monosaccharide in the diet has increased accordingly but 1974 per capita daily consumption of this monosaccharide from all sources was only 6 g and no higher than in 1925-29, when apples provided a larger contribution than at present. High-fructose corn syrups are predicted to increase in production and to replace sucrose and invert sugar in up to 30 percent of their applications by 1980-85, based largely on relative costs. There is no evidence that such replacement, per se, would have an adverse effect on public health.

However, the Select Committee has expressed concern in its report on sucrose (73) that this sugar contributes to dental caries in the public at current consumption levels as used in the manner now practiced. It is questionable that replacement of sucrose by syrups and sugars derived from starch would greatly change the cariogenicity of foods containing these sugars. Informing the consumer of the sugar content of foods by appropriate labeling could lead to judicious use of sweetened foods. Choices could be made easier with a greater selection of less sugared foods in the market place.

The Select Committee has weighed all of the foregoing and concludes that:
Evidence exists that simple sugars, including glucose and fructose [and, therefore, corn sugar (dextrose), corn syrup including high-fructose corn syrup, and invert sugars] are cariogenic. However, in the quantities that these simple sugars are now consumed in processed foods, their contribution to formation of dental caries should be relatively small. If increased usage should occur, as seems likely, the contribution of these sugars to the occurrence of dental caries might become more important.

Other than the contribution made to dental caries, there is no evidence in the available information on corn sugar (dextrose), corn syrup, and invert sugar that demonstrates a hazard to the public when they are used at levels that are now current and in the manner now practiced. However, it is not possible to determine without additional data, whether an increase in consumption—that would result if there were a significant increase in the total of corn sugar, corn syrup, invert sugar and sucrose added to foods—would constitute a dietary hazard.
VI. REFERENCES CITED


44. Cappellato, M. 1942. Sui sarcomi sperimentali da glucosio nel ratto bianco. Tumori 38-52. (Translation supplied with reference no. 1.)


68. Grunberg, E., G. Beskid, and M. Brin. 1973. Xylitol and
dental caries. Efficacy of xylitol in reducing dental caries in

69. Shaw, J.H., L. Krumins, R.J. Gibbons. 1967. Comparison
of sucrose, lactose, maltose and glucose in the causation of

70. Rosen, S. 1969. Comparison of sucrose and glucose in the
14:445-450.

Program and abstracts, 52nd annual meeting, National Association
for Dental Research. (Abstract 604).

and a hydrogenated starch derivative on dental caries in the rat.

73. Select Committee on GRAS Substances. 1976. Evaluation of the
the health aspects of sucrose as a food ingredient (SCOGS-69). Life
Sciences Research Office, Federation of American Societies for
Experimental Biology, Bethesda, Md.
VII. SCIENTISTS CONTRIBUTING TO THIS REPORT

1. Members of the Select Committee on GRAS Substances:

Joseph F. Borzelleca, Ph.D., Professor of Pharmacology, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond, Va.

Harry G. Day, Sc.D., Professor Emeritus of Chemistry, Indiana University, Bloomington, Ind.

Samuel J. Fomon, M.D., Professor of Pediatrics, College of Medicine, University of Iowa, Iowa City, Iowa.

Bert N. La Du, Jr., M.D., Ph.D., Professor and Chairman, Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Mich.

John R. McCoy, V.M.D., Professor of Comparative Pathology, New Jersey College of Medicine and Dentistry, Rutgers Medical School, New Brunswick, N.J.

Sanford A. Miller, Ph.D., Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, Cambridge, Mass.

Gabriel L. Plaa, Ph.D., Professor and Chairman, Department of Pharmacology, University of Montreal Faculty of Medicine, Montreal, Canada.

Michael B. Shimkin, M.D., Professor of Community Medicine and Oncology, School of Medicine, University of California, San Diego, La Jolla, Calif.

Ralph G. H. Siu, Ph.D., Consultant, Washington, D.C.

John L. Wood, Ph.D., Distinguished Service Professor, Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tenn.

George W. Irving, Jr., Ph.D. (Chairman), Research Associate, Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Md.
2. LSRO staff:

C. Jelleff Carr, Ph.D., Director
Kenneth D. Fisher, Ph.D., Associate Director
Richard G. Allison, Ph.D., Research Associate
Samuel B. Detwiler, Jr., Research Associate
Andrew F. Freeman, Research Associate
Frederic R. Senti, Ph.D., Research Associate
John M. Talbot, M.D., Research Associate

The Select Committee expresses its appreciation to the following technical experts and organizations who contributed information and data:


Edmond G. Vanden Bosche, D.D.S., Associate Professor, Fixed Restorative Dentistry, University of Maryland, School of Dentistry, Baltimore College of Dental Surgery, Baltimore, Md. 21202.

Report submitted by:

October 5, 1976

Date

George W. Irving, Jr., Chairman
Select Committee on GRAS Substances
Two requests for a hearing were received and the following individual made a presentation.

Mr. Robert C. Liebenow, President, Corn Refiners Association, Inc.
1001 Connecticut Ave., N.W., Washington, D.C. 20036

The request from Mr. Bendt Bladel, Technical Director, National Confectioners Association of the United States, 36 South Wabash Avenue, Chicago, Illinois 60603, was withdrawn.