DIETARY SUGARS IN HEALTH AND DISEASE

III. SORBITOL

March 1979

Prepared for

BUREAU OF FOODS
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D.C. 20204

under

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by

Richard G. Allison, Ph.D.

LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 Rockville Pike
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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This technical report was prepared for the Bureau of Foods, Food and Drug Administration (FDA), by Richard G. Allison, Ph.D., Staff Scientist, LSRO, FASEB, in accordance with the provisions of Contract No. FDA 223-75-2090.

The LSRO acknowledges the contributions of the investigators who provided data and the consultants who reviewed the draft of the report. However, the listing of consultants' names in Section VII does not imply that they endorse the conclusions of the study. The LSRO accepts the responsibility for the report and the opinions expressed.

The report was 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 report was approved and transmitted to FDA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent societies.

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
SUMMARY

This report on sorbitol is the third in a series on refined carbohydrates in the diet. Technical and scientific data are reviewed in relation to the health aspects of using sorbitol as a food ingredient. Sorbitol is a hexahydric alcohol occurring naturally in many fruits and in many animal tissues. As a food ingredient, sorbitol serves as a humectant, sweetening and flavoring agent, formulating aid, and pickling agent in addition to providing other technical functions. The per capita daily consumption of sorbitol as a food ingredient is about 200 mg.

The results of most studies in experimental animals are consistent with the conclusion that sorbitol is less cariogenic than glucose, sucrose, or fructose. Animal feeding studies and in vitro tests suggest that sorbitol is not mutagenic, teratogenic, or carcinogenic. Inconsistent findings of serum calcium elevation and tissue calcification, altered weights of thyroid and parathyroid glands, adrenal medullary hyperplasia, and possible pituitary chromophobe cell hyperplasia in long-term rat feeding studies at high dietary levels of sorbitol remain unconfirmed and unexplained.

Absorption of sorbitol by human beings is limited by its rate of diffusion from the gastrointestinal tract and by laxation which may occur after ingestion of 25 to 50 g of sorbitol by adults or about 10 g by infants. Absorbed sorbitol is of equivalent caloric value to sucrose, on a weight basis, because the liver metabolizes sorbitol to fructose, glucose, and normal products of carbohydrate metabolism. Ingested sorbitol appears to enter and to be metabolized by only hepatic tissue. Parenterally administered sorbitol can be metabolized by adult human beings at a rate of about 0.25 g per kg body weight. Clinically, blood glucose levels and insulin response are lower after single oral doses of sorbitol than after similar doses of glucose or sucrose. However, data on these parameters from studies of healthy persons and patients with diabetes mellitus who regularly consume sorbitol in their diets are not currently available. Effects of sorbitol on the absorption and/or retention of certain nutrients as well as osmotic disturbances in the gastrointestinal tract may impose limits on the dietary level of sorbitol that can be tested meaningfully in experimental animals or ingested safely by human beings.
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I. INTRODUCTION

A. BACKGROUND

The Bureau of Foods, Food and Drug Administration (FDA), has a continuing interest in and responsibility for the nutritional quality of the United States dietary. The Bureau is responsible for evaluating and monitoring the safety of foods, establishing regulations, and providing nutrition information to consumers.

In keeping with these responsibilities, the FDA requested that the Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), review current scientific information and technologic developments related to the use of sorbitol in foods. This report is the third in a series on dietary sugars in health and disease prepared for FDA by the LSRO. Previous reports have addressed the use in foods of fructose (Kimura and Carr, 1976) and xylitol (LSRO, 1978).

The Code of Federal Regulations [21 CFR 184.1835] lists sorbitol as a Generally Recognized as Safe (GRAS) substance and gives guidelines for the use of sorbitol as a food ingredient including: the categories of foods to which it may be added; the physical or technical functional effects for which it may be added; and the levels of addition that reflect good manufacturing practice. Sorbitol has been the subject of several changes in the Code of Federal Regulations since the GRAS list was established in 1958. In 1961, sorbitol was permitted as a stabilizer and nutritive sweetener in nonstandardized frozen desserts for special dietary use, in amounts not to exceed 15 g per average serving or more than 40 g of sorbitol daily (Office of the Federal Register, 1961). If an average serving provided 5 g or more of sorbitol, a label statement was required disclosing the amount of sorbitol per serving. The requirement of a label warning that the consumption of more than 15 g of sorbitol at one time or more than 40 g of sorbitol per day may have laxative effects was rescinded (Office of the Federal Register, 1962) and later reinstated as it currently exists (Office of the Federal Register, 1974). If consumption of a sorbitol-containing food may result in ingestion of 50 g of sorbitol, regulations [21 CFR 184.1835] require the label statement: "Excess consumption may have a laxative effect."

After removal of cyclamates from the GRAS list, FDA permitted the combination of nutritive and nonnutritive sweeteners in "diet beverages" (Office of the Federal Register, 1970a). That regulation [21 CFR 100.130] considers the possibility "...of injury through the inadvertent use by diabetics in the belief that the product does not contain carbohydrates..." and requires the label of a beverage containing sorbitol, mannitol, or other hexitol to bear the statement: "Contains carbohydrates, not for use
by diabetics without advice of a physician." The labels of beverages containing xylitol and other polyols are not permitted to bear statements such as "sugar free," "sugarless," "no sugar," or similar statements. Regulations in 1970 permitted the use of sorbitol in combination with saccharin in canned fruits for a period of 1 year; this period was not extended (Office of the Federal Register, 1970b).

Sorbitol was affirmed as a GRAS ingredient (Office of the Federal Register, 1974) pursuant to an FDA review of the safety of GRAS and prior-sanctioned food ingredients. As part of this review, the LSRO Select Committee on GRAS Substances (Select Committee) had evaluated the health aspects of sorbitol as a food ingredient (Select Committee, 1972). After completion of the FDA review of the GRAS status of sorbitol, several developments reflected heightened interest in sorbitol: the results of additional animal feeding experiments involving the safety and efficacy of sorbitol became available; the FDA was petitioned to establish a standard of identity for sorbitol-sweetened dietary jams; and, the marketing of foods containing combinations of sorbitol and nonnutritive sweeteners, such as saccharin-sorbitol frozen desserts, was suggested (Anonymous 1976a,b; 1978).

B. SCOPE

This report reviews technical and scientific data on sorbitol in relation to its role as a food ingredient and to the health effects of use of sorbitol in foods. It focuses on selected references and recent research on safety, metabolic, and pharmacokinetic aspects of sorbitol administered both parenterally and orally to man and experimental animals. Sources of information include reviews of the use of sorbitol by the Joint FAO/WHO Expert Committee on Food Additives (1964, 1974, 1978) and the Select Committee (1972); recent reports related to polyol and carbohydrate metabolism (Fisher et al., 1977; Kimura, 1977; Taibot, 1978); the computerized literature citation retrieval systems of the National Library of Medicine; as well as compilations of literature from industrial laboratories. Additional literature references, data, and opinions were supplied by consultants and current investigators of sorbitol metabolism.
II. PROPERTIES, OCCURRENCE, MANUFACTURE, AND USE

A. CHEMICAL AND PHYSICAL PROPERTIES

Sorbitol, C\textsubscript{6}H\textsubscript{14}O\textsubscript{6}, is the common name for D-glucitol (CAS Registry No. 3959-53-3), a naturally occurring hexahydric alcohol in plants and animals (Wright, 1974). Often referred to as a polyol, sugar alcohol, or hexitol, sorbitol is a reduced carbohydrate produced commercially by catalytic hydrogenation of glucose and invert sugar. It is about 35 to 60 percent as sweet as sucrose (w/w) (Moskowitz, 1971; Wright, 1974). The configurational relationship of certain substances mentioned in this report can be seen in structural formulas presented here for reference:

```
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CHO} & \quad \text{CH}_2\text{OH} \\
\text{HCOH} & \quad \text{HCOH} & \quad \text{HOCH} & \quad \text{HCOH} & \quad \text{C}=\text{O} \\
\text{HOCH} & \quad \text{HOCH} & \quad \text{HOCH} & \quad \text{HOCH} & \\
\text{HCOH} & \quad \text{HCOH} & \quad \text{HCOH} & \quad \text{HCOH} & \\
\text{HCOH} & \quad \text{HOCH} & \quad \text{HCOH} & \quad \text{HCOH} & \\
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \quad \text{CH}_2\text{OH} & \\
\end{align*}
```

D-Sorbitol    L-Iditol    D-Mannitol    D-Glucose    D-Fructose

Sorbitol crystallizes with one-half or one molecule of water and these forms melt at 110 to 112°C and 75°C, respectively (Weast, 1978). Commercially available sorbitol is metastable and its melting point is dependent on the degree of hydration of the sample (Griffin and Lynch, 1972; Merck Index, 1976). Food grade sorbitol occurs as white, hygroscopic powder, flakes, or granules; specifications are given in the Food Chemicals Codex (National Research Council, 1972). The solubility of sorbitol in ethanol, methanol, and acetic acid is slight, but 1 g will dissolve in 0.45 ml of water. Mannitol and other polyhydric alcohols may be present in small amounts but assay must be not less than 91 percent sorbitol. Sorbitol may contain not more than 3 ppm arsenic (as As), 50 ppm chloride, 10 ppm heavy metals (as Pb), 0.3 percent reducing sugars, 100 ppm sulfate, and 1 percent total sugars. Not more than 1 percent is lost on drying, and the residue on ignition is not more than 0.1 percent (National Research Council, 1972).

Food grade sorbitol solution contains between 29 and 31 percent water, assays not less than 64.0 percent sorbitol, and has a specific gravity of at least 1.285 (National Research Council, 1972). The solution may contain not more than 3 ppm
arsenic (as As), 50 ppm chloride, 10 ppm heavy metals (as Pb),
100 ppm sulfate, 0.21 percent reducing sugars, 0.7 percent total
sugars, and a residue on ignition of not more than 0.1 percent.
The sweet-tasting solution is a clear, colorless, syrupy liquid.
It is neutral to litmus and miscible with glycerin and with prop-
ylene glycol.

The following values are representative of a commer-
cial 70-percent solution of sorbitol: \(d_{20}^\circ = 1.2879; n_{25}^\circ = 1.45831;\)
\([\alpha]_D^\circ = -2.10^\circ\); pH between 6 and 7; and viscosity at 25°C = 110
centipoises (Merck Index, 1976). An aqueous solution of sorbitol
is more viscous than an aqueous solution of glycerol at the same
concentration.

The absence of an aldehyde or keto group, which might
participate in browning (Maillard) reactions and affect color and
flavor during processing and storage, contributes to the stability
and value of sorbitol and other polyols in food products. No Maill-
lard type reaction would be expected to occur between sorbitol and
free amino groups present in proteins, amino acids, certain vita-
mins, and other food constituents. If kept cold, sorbitol is
resistant to degradation by dilute acid, alkali, or mild oxidizing
agents (Wright, 1974).

B. COMMERCIAL PRODUCTION

The commercial production of sorbitol began in 1937 with
batch electrochemical reduction of glucose and by 1948 had pro-
gressed to electrochemical and catalytic reduction in a continuous
flow process (Sunshine, 1973; Wright, 1974). Sorbitol is produced
commercially from aqueous glucose solutions at 120 to 160°C and
hydrogen pressures of 70 to 140 atmospheres in the presence of a
supported nickel or Raney nickel catalyst. Little isomerization
of sorbitol occurs under acid hydrogenation conditions or when
hydrogen or catalyst is absent. However, other hexitols are
formed under alkaline conditions, and the commercially useful hexi-
tols, sorbitol and mannitol, can be interconverted. The hydrogena-
tion of fructose produces equal amounts of sorbitol and mannitol.
Mannitol is less soluble than sorbitol and can be removed by crys-
tallization. The hydrogenation of invert sugar at neutral pH
yields 25 percent mannitol and 75 percent sorbitol because the
rate of hydrogenation of fructose is about an order of magnitude
faster than hydrogenation of glucose. Thus, the proportion of man-
nitol formed during hydrogenation of invert sugar can be increased
under alkaline conditions that permit the isomerization of glucose
to fructose (Wright, 1974).
C. COMMERCIAL UTILIZATION

1. Nonfood uses.

Sorbitol is used commercially in the manufacture of sorbose, ascorbic acid, propylene glycol, synthetic plasticizers and resins, and emulsifying agents (anhydrosorbitol fatty acid esters and polyoxyethylene anhydrosorbitol fatty ether esters) (Sunshine, 1973; Wright, 1974). It improves flow properties of writing inks and serves as a humectant in leather and tobacco. Certain antifreeze mixtures contain sorbitol with glycerol or glycols. As a vehicle for vitamins, sorbitol may improve absorption and utilization of vitamin B₁₂, but conflicting data exist. Sorbitol is used in mouthwash and toothpaste because it resists fermentation by microorganisms. Less sorbitol than crystalline mannitol is employed as an ingredient in antacids, aspirin, coughdrops, chewable vitamin tablets, and chewing gums (Anonymous, 1977; Wright, 1974).

2. Food applications.

The relative sweetness of equal concentrations in water of sorbitol compared with 1M and 1 percent glucose is 0.53 and 0.50, respectively (Moskowitz, 1971). By contrast, 1M sucrose is 3.20 times as sweet as 1M glucose, and 1 percent sucrose is 1.40 times as sweet as 1 percent glucose. From these data, 1-percent sorbitol solution would be about 35 percent as sweet as a 1-percent sucrose solution. Such comparisons of relative sweetness in water solutions do not correspond to perceived sweetness in food products, nor would adjustment to equal sweetness necessarily result in equal acceptability of the products (Moskowitz, 1974). Nearly three times the calories would be provided by sorbitol as by sucrose to achieve equal sweetness because equal weights of sucrose and sorbitol provide approximately equal caloric value (Arvidsson Lenner, 1976; Bassler, 1974; Staub, 1978). A role for sorbitol in formulating foods with reduced caloric values appears to be limited and to be dependent on its combination with nonnutritive sweeteners; recent tests indicated that fructose-saccharin-sweetened citrus base soft drinks were regarded "better" than commercial soft drinks sweetened with either saccharin or a mixture of sorbitol and saccharin (Hyvonen et al., 1978).

Technical effects rather than sweetness account for addition of sorbitol to many foods. Sorbitol serves as a humectant, flavoring agent and adjuvant, formulation aid, pickling agent, emulsifier and emulsifier salt, firming agent, lubricant and release agent, sequestrant, stabilizer and thickener, surface-finishing agent, and texturizer [21 CFR 184.1835]. The first three effects listed, together with its sweetening function, were those most frequently reported in an NAS Survey of 1970 industrial usage of sorbitol (National Academy of Sciences, 1972).
The humectant properties of sorbitol are of value in extending the shelf-life of shredded coconut and marshmallows (Wright, 1974). Sorbitol incorporated in candies such as fudge and mint creams retards the crystallization of sucrose. In sorbitol-containing ice cream, chocolate, and chewing gum, sorbitol serves as a sweetener to replace sucrose. Such foods are sometimes labeled "dietetic" on the basis that potentially less of a hyperglycemic response may result from the slower-absorbed sorbitol compared with glucose or sucrose. Other factors discussed later, such as altered patterns of glycogen deposition or reduced gluconeogenesis, may contribute to differences in blood glucose patterns observed after oral and parenteral administration of sorbitol (Froesch et al., 1971).

The level of sorbitol that may be added to various categories of processed foods is limited according to guidelines in 21 CFR 184.1835(d) (Table 1). Accurate estimates of the average intakes of sorbitol by individuals in the United States are not available. However, the average portion size and the permitted levels of addition can be utilized to calculate the intake from eating one portion of a food containing sorbitol at the maximum permitted level. This intake ranges up to 40 g sorbitol per portion in the case of soft candy. Addition of the intakes in Table 1 across categories is not an appropriate means of estimating an average intake. Most foods in the listed categories do not contain added sorbitol, and it seems unlikely that an average person would consume sorbitol-containing products from each of the food categories in Table 1 on a given day. Surveys of food processors indicated the daily per capita consumption of sorbitol was about 80 mg in 1970 and three times this amount in 1975 (Committee on GRAS List Survey--Phase III, 1978; Subcommittee on Review of the GRAS List--Phase II, 1972). Thus, a person who eats just one portion of a food containing sorbitol at the levels shown in Table 1 consumes an amount of sorbitol that is 10 to 200 times the U.S. per capita daily consumption. Clearly, additional food consumption data are needed before estimating average and higher percentile intakes of sorbitol for persons who eat sorbitol-containing products.

D. NATURAL OCCURRENCE

Sorbitol is widely distributed in plants and animals. Free sorbitol is present in pears, peaches, plums, cherries, apples, and berries as well as various seaweeds (Griffin and Lynch, 1972; Washützl et al., 1973). Sorbitol is a normal metabolite of glucose and is present in many animal fluids and tissues at low concentrations. Some representative levels of sorbitol in tissues and fluids of rats and human beings, normal and diabetic, are presented in Table 2. In diabetes mellitus, the levels of both sorbitol and fructose (formed from sorbitol) increase in those tissues, often referred to as "insulin-independent," in which the amount of intracellular glucose available for enzymatic
TABLE 1. Calculation of the intake of sorbitol resulting from consuming one portion of a processed food containing sorbitol at the maximum permitted level.

<table>
<thead>
<tr>
<th>Food category</th>
<th>Maximum level</th>
<th>Portion size</th>
<th>Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>percent</td>
<td>grams</td>
<td>grams</td>
</tr>
<tr>
<td>Hard candy and cough drops</td>
<td>99</td>
<td>28.3</td>
<td>28.0</td>
</tr>
<tr>
<td>Soft candy</td>
<td>98</td>
<td>42.3</td>
<td>41.5</td>
</tr>
<tr>
<td>Chewing gum</td>
<td>75</td>
<td>3.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Commercial, nonstandardized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>jams and jellies</td>
<td>30</td>
<td>35.7</td>
<td>10.7</td>
</tr>
<tr>
<td>Baked goods and baking mixes</td>
<td>30</td>
<td>51.6</td>
<td>15.5</td>
</tr>
<tr>
<td>Frozen dairy desserts</td>
<td>17</td>
<td>111.6</td>
<td>19.0</td>
</tr>
<tr>
<td>All other categories</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Defined in 21 CFR 170.3(n).  
21 CFR 184.1835(d).  
USDA mean portion size for age groups 2-65+ years (Subcommittee on Review of the GRAS List--Phase II, 1972).  
It is unlikely that anyone would consume products containing sorbitol from each of these food categories on any given day, so it would be inappropriate to estimate average daily intakes by adding these values.  
This portion size was estimated by the Subcommittee on Review of the GRAS List--Phase II (1972).
TABLE 2. Representative concentrations of sorbitol in certain fluids (mmol per l) and tissues (mmol per kg wet weight) of rats and human beings.

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic</th>
<th>Diabetic</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rat:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>0.02±0.002</td>
<td>0.09±0.004&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Stewart et al., 1967</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>0.02±0.002</td>
<td>0.12±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Sciatic nerve</td>
<td>0.15±0.008</td>
<td>3.46±1.53&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ward et al., 1972</td>
</tr>
<tr>
<td>Peripheral nerve</td>
<td>0.23±0.03</td>
<td>1.69±0.19</td>
<td>van Heyningen, 1962</td>
</tr>
<tr>
<td>Lens</td>
<td></td>
<td>22</td>
<td>Morrison et al., 1970</td>
</tr>
<tr>
<td>Plasma</td>
<td>0.005</td>
<td></td>
<td>&quot;</td>
</tr>
<tr>
<td>Pancreatic islet</td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Human:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seminal plasma</td>
<td>5.5 - 11</td>
<td></td>
<td>Mann, 1946</td>
</tr>
<tr>
<td>Blood plasma</td>
<td></td>
<td>0.1</td>
<td>Wray &amp; Winegrad, 1966</td>
</tr>
<tr>
<td>Blood plasma</td>
<td>2.3±0.2 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
<td>14. - 44 x 10&lt;sup&gt;-3&lt;/sup&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Morrison et al., 1970</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>11.5±0.5 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
<td>45.3±34.1 x 10&lt;sup&gt;-3&lt;/sup&gt;&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Pitkänen &amp; Servo, 1973</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>17.2±4.6 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
<td>44.2±16.1 x 10&lt;sup&gt;-3&lt;/sup&gt;&lt;sup&gt;e&lt;/sup&gt;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Urine</td>
<td>33.2±19.8 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
<td>29.4±12.9 x 10&lt;sup&gt;-3&lt;/sup&gt;</td>
<td>Ward et al., 1972</td>
</tr>
<tr>
<td>Peripheral nerve</td>
<td></td>
<td>0.52</td>
<td>Heaf &amp; Galton, 1975</td>
</tr>
<tr>
<td>Lens (cataract)</td>
<td>0.28±0.08</td>
<td>0.46±0.09</td>
<td>Pirie &amp; van Heyningen, 1964</td>
</tr>
<tr>
<td>Lens</td>
<td>&lt;0.1</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Alloxan.<br>
<sup>b</sup>Streptozotocin.<br>
<sup>c</sup>Range estimated from plotted data.<br>
<sup>d</sup>Insulin-dependent.<br>
<sup>e</sup>Adult onset.
reduction to sorbitol is directly related to blood glucose levels (Winegrad et al., 1972). Consequently, the intracellular concentration of sorbitol in these tissues is influenced by the effect of insulin on blood glucose levels.
III. ABSORPTION AND METABOLISM

A. ABSORPTION

1. Sorbitol absorption.

The absorption of sorbitol given orally as a single dose to fasted animals is slower and less complete than that of glucose. The absorption of 90 percent of 300 mg of sorbitol by 250-g female rats required more than 3 hours compared to less than 1 hour for glucose (Wick et al., 1951). This slow rate of absorption could account for the lower rise in blood glucose levels after sorbitol than after glucose feeding. It is probably a contributing factor to the laxative effect reported for excessive doses of sorbitol in animals and in individuals consuming more than 40 or 50 g per day (Ellis and Krantz, 1941; Peters and Lock, 1958). Most studies have focused on metabolic aspects subsequent to absorption; thus the effect of other foods on the absorption rate of sorbitol is not well established in normal or diabetic animals and human beings (Vaaler et al., 1978).

Adcock and Gray (1957) administered 35 g of sorbitol in 250 to 300 ml of water to normal and diabetic subjects who had fasted overnight or for 3 hours prior to treatment. The blood glucose level of normal subjects was not significantly affected; however, diabetic subjects had a significant increase in blood glucose concentrations ranging from 9 to 49 mg per dl. It should be noted, however, that the increase in blood glucose levels of diabetic subjects was less than the increase after they ingested an equal dose of glucose. Sorbitol was not detectable in blood samples of either group by a method sensitive to 2 to 3 mg per dl, but a 50-g dose of sorbitol produced a blood concentration of 9 mg per dl of sorbitol in one normal subject after 1 hour. Normal and diabetic subjects eliminated less than 3 percent of the dose in the urine and no detectable amount in the feces. After administration of antibiotics, up to 10 percent of ingested sorbitol was found in the feces. The radioactivity of uniformly labeled sorbitol given orally to one normal and one diabetic subject was recovered largely (80 percent) in expired air, while one "severe diabetic" subject expired only 65 percent and excreted 9 percent in the urine, presumably as labeled glucose (Adcock and Gray, 1957).

2. Absorption of other nutrients.

Both mice and rats showed enlarged ceca after consuming diets containing 15 percent sorbitol, and the syntheses of B vitamins by gut bacteria increased (Griem and Lang, 1960; Morgan and Yudkin, 1959). However, sorbitol did not spare B vitamins in these species in the absence of coprophagy. Urinary excretion of thiamin, riboflavin, and N'-methylnicotinamide was increased in
one man who consumed 20 to 40 g of sorbitol daily for 6 weeks. It was not possible to differentiate between enhanced absorption of dietary vitamins and the possibility of increased synthesis with subsequent absorption (Watson and Yudkin, 1959). At any rate, the increases were very small when compared with the recommended dietary allowances (National Research Council, 1974).

Conflicting reports exist on the effects of sorbitol on the absorption of vitamin B₁₂. The difference appears to be related to the dosage of both sorbitol and vitamin B₁₂. In rats, large doses of sorbitol enhanced the absorption of large doses of vitamin B₁₂; however, Okuda (1961) reported that a large dose of sorbitol inhibited absorption of physiological amounts of vitamin B₁₂. In human beings, the absorption of vitamin B₁₂ from a 0.5-μg dose was reduced in 30 percent of persons tested after oral administration of 10 g of sorbitol (Heinrich and Staak, 1960). Intrinsic factor reversed this effect unless the sorbitol intake exceeded 30 g. Other investigators found sorbitol to increase absorption of therapeutic doses, 30 to 50 μg, and in some cases physiologic doses, 2 μg, of vitamin B₁₂ by healthy persons but of little or no value in treating pernicious anemia patients without intrinsic factor (Boger et al., 1959; Chow et al., 1959; Greenberg et al., 1957; Herbert et al., 1959).

Sorbitol enhanced the absorption of iron, strontium, and calcium in feeding studies with rats (Fournier et al., 1967; Herndon et al., 1958). When the dietary level of sorbitol was 16 percent, calcium absorption was enhanced and large amounts of citric acid and calcium were excreted in the urine. Moreover, hypercalcemia, bladder concretions, and thickening of the skeleton were described. At 6 percent of the diet, sorbitol also increased calcium retention (Fournier et al., 1955).

B. METABOLISM

1. Endogenous sorbitol.

A brief discussion of the metabolism of endogenous sorbitol is included here for completeness, but sorbitol consumed in foods apparently does not enter tissues other than the liver and does not directly influence the metabolism of endogenous sorbitol in other tissues. The metabolic pathway by which glucose is converted to sorbitol and subsequently to fructose in animals is shown in Figure 1.

Endogenous sorbitol is produced from glucose by aldose reductase, an NADPH-dependent enzyme capable of catalyzing the reduction of many different aldoses, which is widely distributed in body tissues (Winegrad et al., 1972). The importance of variations in the activity and distribution of aldose reductase in relation to cell type and complications of diabetes mellitus has been reviewed by Gabbay (1973).
Aldose reductase has a low affinity for glucose and galactose \((K_m = 20 \text{ to } 150 \text{ mM})\) and the amount of sorbitol formed is related to intracellular glucose concentration. Free glucose is present in the tissues of normal animals because it is transported into the cells at a rate exceeding its phosphorylation by hexokinase (Winegrad et al., 1972). The effect of insulin on blood glucose levels normally would restrict the availability of intracellular glucose and thus limit the activity of aldose reductase to a low level. However, the intracellular availability of free aldose in insulin-independent tissues can increase due to higher blood levels in diabetes mellitus and galactosemia so that significant synthesis of sorbitol and galactitol may occur. Because most tissues are essentially impermeable to the sugar alcohols, their accumulation may result in increased osmotic pressures of 10 to 80 milliosmolar. This has been reported for lens, sciatic nerve, and renal papilla (Gabbay, 1973; Kinoshita, 1976; Spiro, 1976). The osmotic effect from accumulation of sorbitol, accompanied by altered concentrations of amino acids, sodium and potassium ions, and myoinositol, is considered a major factor in cataract development in diabetic persons. Lenses from persons with diabetes mellitus generally contained more sorbitol and fructose than those from nondiabetic patients (Heaf and Galton, 1975; Pirie and van Heyningen, 1964). However, a definite cause and effect relationship between sorbitol accumulation and cataract development or decreased nerve function, as may occur in persons with diabetes mellitus, has not been established clinically or experimentally (Gabbay, 1973; Mehnert, 1978; Touster, 1974).

Sorbitol is oxidized to D-fructose by sorbitol dehydrogenase (L-iditol dehydrogenase). This is an NAD-dependent enzyme with broad substrate specificity capable of dehydrogenating sorbitol, xylitol, ribitol, L-iditol, allitol, L-gala-D-gluco-heptitol, and D-altro-D-gluco-heptitol (McCorkindale and Edson, 1954). All mammalian species thus far examined contain this enzyme in their liver (Winegrad et al., 1972). Other human tissues having this activity include prostate, kidney, spleen, vascular tissue, and testes; very low activities are found in cardiac and skeletal muscle. Aldose reductase and sorbitol dehydrogenase constitute the enzymes responsible for the synthesis of fructose in seminal fluids (Hers, 1956). Mann and Parsons (1950) have demonstrated an increased concentration of fructose in seminal fluid in response to the elevation of blood glucose in alloxan-diabetic rabbits. The concentrations of fructose and sorbitol in the brain, spinal cord, and sciatic nerve of rats were related linearly to blood glucose levels (Gabbay et al., 1966). This pathway of glucose metabolism normally accounts for a small fraction of glucose utilization but it appears to operate at unimpaired or increased rates during insulin deficiency (Gabbay, 1973; Winegrad et al., 1972).

The physiological significance of a pathway for fructose synthesis in lenses and peripheral nerves is of interest because fructose does not appear to be a preferred substrate for glycolysis in these tissues as it is in spermatozoa (Winegrad et al.,
FIGURE 1. Schematic diagram of hepatic metabolism of sorbitol and related carbohydrates.

Reaction number, enzyme nomenclature, and Enzyme Commission number: 1, aldose reductase, (1.1.1.21); 2, glucokinase, (2.7.1.2); 2', glucose-6-phosphatase, (3.1.3.9); 3, glucosephosphate isomerase, (5.3.1.9); 4, 6-phosphofructokinase, (2.7.1.11); 4', hexose-diphosphatase, (3.1.3.11); 5, fructose-bisphosphate aldolase, (4.1.2.13); 6, triosephosphate isomerase, (5.3.1.1); 7, L-iditol dehydrogenase (sorbitol dehydrogenase), (1.1.1.14); 8, ketohexokinase, (2.7.1.3); 9, fructose-bisphosphate aldolase, (4.1.2.13); 10, triokinase, (2.7.1.28); 11, aldehyde dehydrogenase (1.2.1.3); 12, glycerate kinase, (2.7.1.31); 13, glycerol dehydrogenase (NADP), (1.1.1.72), or alcohol dehydrogenase (NAD), (1.1.1.1); 14, lactate dehydrogenase, (1.1.1.27).

Abbreviations: NAD = nicotinamide adenine dinucleotide; NADH = reduced NAD; NADP = NAD phosphate; NADPH = reduced NADP; ATP = adenosine triphosphate; ADP = adenosine diphosphate; — — — → indicates multistep pathway.

1972). Gabbay and Tze (1972) have suggested a physiological role for sorbitol formation in the pancreas where sorbitol formation may be an essential preliminary step in insulin release; however, Malaisse et al. (1976) suggested that the sorbitol pathway plays a small role, if any, in the process of glucose-induced insulin release. The latter investigators found higher concentrations of sorbitol in rat islets incubated with β-D-glucose than in islets incubated with the more insulinotropic α-D-glucose.

2. Exogenous sorbitol.

Exogenous sorbitol does not readily enter tissues other than the liver even after parenteral administration and is not metabolized by heptectomized animals (Wick and Drury, 1951). Orally and parenterally administered sorbitol is absorbed and metabolized in mammalian liver largely via a pathway located entirely in the cytoplasmic compartment (Figure 1). The uptake of sorbitol by the liver, the initial steps in its metabolism, and its conversion to glucose are not regulated by or independent on insulin (Dwivedi, 1976; Keller and Froesch, 1972; Winegrad et al., 1972). However, the utilization of ingested sorbitol as an energy source by peripheral tissues, muscle, and adipose tissue is via its hepatic metabolic products, mainly glucose, and thus subject to the influence of insulin (Winegrad et al., 1972).

Sorbitol is first oxidized to fructose by sorbitol dehydrogenase (Hers, 1955, 1960; Touster, 1975). There is no evidence for the direct oxidation of sorbitol to glucose by aldose reductase (Winegrad et al., 1972). Phosphorylation by ketohepxokinase yields fructose 1-phosphate that is split to dihydroxyacetone phosphate and glyceraldehyde. Dihydroxyacetone phosphate derived from splitting of fructose 1-phosphate may be metabolized in glycolysis through pyruvate or, during gluconeogenesis, to glucose and glycogen. The metabolism of sorbitol has been studied recently in cultured rat liver cells. Rat liver hepatocytes in primary culture converted sorbitol to numerous metabolic intermediates including, among others identified by paper chromatography: fructose 6-phosphate and fructose 1,6-diphosphate; glucose and glucose 6-phosphate; 3-phosphoglyceric acid; glucuronic acid; phospho(enol) pyruvate; glycerol 3-phosphate; citric, malic, fumaric, and lactic acids; and glutamine, alanine, glutamic acid, and aspartic acid (Levine et al., 1978). Rat hepatoma-derived cultured cells (HTC), on the other hand, lack the ability to phosphorylate sorbitol and/or the ability to convert fructose 1-phosphate to triose phosphates and did not convert sorbitol and fructose to these intermediates. When incubated in 5 mM [U-14C]glucose, HTC cells accumulated sorbitol and fructose with sorbitol appearing first. An equilibrium was reached in which the concentration of fructose was about twice that of sorbitol. Hepatocytes in primary culture did not accumulate detectable levels of labeled sorbitol or fructose from labeled glucose, indicating that these metabolites may exist in very low concentrations in normal cells (Levine et al.,
This observation is in agreement with the kinetic properties and activities of sorbitol dehydrogenase and ketohexokinase of both rat liver and human livers (Heinz et al., 1968).

It is believed that the main metabolic pathways followed by glyceraldehyde are phosphorylation by triokinase to glyceraldehyde 3-phosphate and oxidation by aldehyde dehydrogenase to glyceraldehyde which is subsequently phosphorylated to 2-phosphoglyceraldehyde (Förster, 1974; Heinz et al., 1968). Glyceraldehyde also can be reduced to glycerol which can be converted by the action of several enzymes to dihydroxyacetone phosphate; Förster (1974) states that the fate of glyceraldehyde is "not quite clear." In fact, the extent to which the different pathways are used depends on the steady state concentrations of glyceraldehyde and the kinetic properties of the involved enzymes. The main pathway of glyceraldehyde metabolism probably is phosphorylation by triokinase (Siller et al., 1969). This data strongly suggested that the reductive pathway of glyceraldehyde metabolism requires parenteral administration in order to achieve high intracellular concentrations of glyceraldehyde.

Several aspects of sorbitol metabolism are addressed as potential problems or as areas that need further clarification. One uncertainty is the metabolic consequences of producing NADH from sorbitol's oxidation in the cytoplasm of the liver cell. Most dehydrogenase reactions occur in the mitochondria where reduced coenzymes are reoxidized by the respiratory process (Winegrad et al., 1972). However, several dehydrogenases, including sorbitol dehydrogenase and alcohol dehydrogenase, function in the cytoplasm rather than in the mitochondria. If the inhibiting action of ethanol on gluconeogenesis results, in part at least, from the accumulation of reduced coenzyme, then sorbitol could have a similar effect. Such an effect would be an important element in defining the capacity of the liver to metabolize sorbitol. For example, the levels of glycerophosphate and lactate in rat liver responded differently to the intraportal infusion of sorbitol and fructose at equivalent rates (Bässler and Stein, 1967). Significantly more glycerophosphate and less lactate are produced from sorbitol than from fructose infusion. However, when ethanol was infused with fructose, the levels of glycerophosphate and lactate approximated those observed after sorbitol infusion alone.

Another question concerns the existence of alternate pathways for the oxidation of sorbitol and the influence of varying physiological conditions and other dietary constituents on its metabolism. Since the 1950's, researchers have reported that sorbitol metabolism appeared to involve a pathway other than its conversion to glucose via fructose (Freedland and Harper, 1959; Wick et al., 1955).

After oral administration of sorbitol (1 g per kg) to alloxan-diabetic rats fed a diet containing 68 percent sucrose or fructose, 40 percent of the sorbitol dose was oxidized by a pathway not involving its conversion to glucose (Wick et al., 1955).
Normal and diabetic rats oxidized similar proportions of orally administered sorbitol in equivalent periods of time. Other investigators (Freedland and Harper, 1959) found increased activity of rat liver glucose-6-phosphatase and fructose-1,6-diphosphatase after fructose was substituted for dietary dextrin (65 percent of diet); however, substitution with sorbitol increased the activity of glucose-6-phosphatase but not of fructose-1,6-diphosphatase. Thus, even though the metabolism of sorbitol involves its initial conversion to fructose in the liver, metabolic and physiologic data suggest subsequent metabolism differs from that of orally administered fructose under these dietary conditions. In addition to suggesting that alternate metabolic pathways exist for sorbitol, Freedland and Harper (1959) cautioned that metabolism of sorbitol might also differ after small and large doses.

Data on the metabolism of sorbitol do not suggest adverse effects or abnormal metabolic conditions are encountered by healthy individuals consuming a normal mixed diet including foods containing sorbitol; however, a potential exists for exceeding the capacities of normal metabolic pathways. This point is best documented by the results of parenteral studies discussed under Safety Evaluation. In regard to oral administration, most experts agree that sorbitol has a caloric value of about 4 kcal per g, similar to that of sucrose (Arvidsson Lenner, 1976; Bässler, 1974; Staub, 1978). This is supported by the ability of sorbitol to substitute for other caloric sources in animal feeding, but attempts to provide a major portion of caloric value of the diet as sorbitol have been influenced by problems of absorption and laxation. Diets of unusual composition may present other problems, such as limited gluconeogenesis (Karimzadegan, 1978).

On the basis of weight gain and changes in the level of plasma ketones, the availability and utilization of sorbitol as a carbohydrate source were estimated to be 50 percent that of glucose for rats maintained on a carbohydrate-free diet containing a high level of free fatty acids (Karimzadegan, 1978). When sorbitol was fed at 1 and 2 percent of an otherwise carbohydrate-free diet, reduced food intake resulted. Under conditions of the test, a limited capacity may exist for absorption and conversion of sorbitol to fructose or for the induction of enzymes necessary for its metabolism. Decreased hepatic utilization of sorbitol from the inhibition of phosphofructokinase by free fatty acids has been suggested as a mechanism to explain accumulation of sorbitol in the livers of rats after infusion of free fatty acids (Beaumont et al., 1971; Stein and Bässler, 1968).
IV. SAFETY EVALUATION

A. ANIMAL STUDIES

1. Parenteral administration.

Following parenteral administration, sorbitol is oxidized by sorbitol dehydrogenase in the cytoplasm of hepatic cells, producing D-fructose and reduced NAD as illustrated in Figure 1. This process is facilitated by the greater permeability of the liver cell membrane for sorbitol compared with other cell membranes (Froesch and Jakob, 1974).

The metabolism of exogenously administered sorbitol in nonhepatic tissues is dependent on entry of sorbitol into the tissue. The metabolism of a small amount of sorbitol by rat adipose tissue in vitro was demonstrated by Crofford et al. (1965). During incubation of epididymal fat pads and adipose tissue cells in 5 mM \(^{14}\text{C}\) sorbitol, addition of insulin increased production of \(^{14}\text{C}\) CO\(_2\) both in the presence and absence of glucose indicating that insulin apparently facilitated sorbitol transport across the cell membrane. In contrast, Froesch and Jakob (1974) found no significant sorbitol dehydrogenase activity in homogenates of adipose tissue and suggested that another enzyme had contributed to the metabolism of sorbitol in isolated adipose tissue observed by Crofford et al. (1965). In the absence of insulin, almost no radioactivity was incorporated into rat diaphragm glycogen and adipose tissue total lipids after intravenous injection of 20 mg of \(^{14}\text{C}\) sorbitol (about 0.1 g per kg body weight) (Froesch et al., 1971). Since insulin administration stimulated carbon-14 incorporation into diaphragm glycogen and total lipids and also resulted in lower blood glucose levels, it appears that parenterally administered sorbitol is converted in the liver to glucose rapidly in comparison to the time required for sorbitol to enter and be metabolized in tissues other than liver.

Froesch et al. (1971) noted that essentially all carbon-14 present in serum was in the form of \(^{14}\text{C}\) glucose within 15 minutes after intravenous injection of 20 mg of \(^{14}\text{C}\) sorbitol. In normal rats in the fed state, the incorporation of radioactivity into liver glycogen had reached a maximum within 10 minutes and the percentage retained in liver glycogen and total lipids was small. This latter observation differed from the response to sorbitol by streptozotocin-diabetic rats which showed greater and more sustained incorporation into liver glycogen and a concomitantly reduced incorporation into total lipids. The incorporation of radioactivity into muscle glycogen and adipose tissue lipids was insulin-dependent in normal and diabetic animals (Froesch et al., 1971).
Fructose, xylitol, and sorbitol, but not glucose, were taken up and metabolized by isolated livers from fasting rats (Förster, 1974). Metabolism of fructose and sorbitol resulted in 15 to 25 percent of the substrate being released as lactate. Glycogen synthesis was minimal. The lactate-pyruvate ratio measured in the liver perfusate was very high for sorbitol, xylitol, and ethanol, minimally affected by fructose, and unchanged by glucose (an increase in the lactate-pyruvate ratio is generally interpreted as a reflection of the NADH-NAD ratio). A rapid return of this ratio to normal values after depletion of sorbitol and xylitol was interpreted as evidence of an effective mechanism for transporting reducing equivalents to the mitochondria. In vivo studies (Lindros, 1970; Lindros and Hillbom, 1969) on fasted male Wistar rats support this view inasmuch as changes in the redox state of the cytoplasm during ethanol oxidation were paralleled by changes in the mitochondrial redox state. These same investigators found that the lactate-pyruvate ratio in the liver cytoplasm of fasted male Wistar rats 15 minutes after an intravenous dose of sorbitol (0.5 g per kg body weight) did not differ from that measured in normal controls. However, the rate of hydrogen transport from the cytoplasm into the mitochondria in the liver may be low when compared with the rate of sorbitol dehydrogenation after intraperitoneal administration (Bässler and Stein, 1967). Bässler (1974) has logically concluded that elevating the NADH-NAD ratio in the cytoplasm by metabolism of sorbitol (also ethanol or xylitol) can affect other metabolic processes and that the extent of the effect is ultimately related to dosage.

Intravenous administration of sorbitol or glucose, 0.4 to 0.8 g per kg per hour to rats for 2 hours, resulted in storage of about 50 percent more glycogen from sorbitol than from glucose (Förster, 1974). Blood glucose levels were more responsive to the rate of glucose infusion while glycogen deposition responded more to the rate of sorbitol infusion. In streptozotocin-diabetic rats glycogen deposition occurred after sorbitol, but not after glucose, infusion; however, the amount of glycogen formed was significantly less than observed in normal animals.

Infusion of normal rats with glucose, fructose, sorbitol, or xylitol at a rate of about 1 g per kg body weight per hour for a 72-hour period caused accumulation of triglycerides in the liver (Machytka et al., 1977). Fructose produced a triglyceride concentration (45 mg per g) twice that produced by glucose, but sorbitol and xylitol administration caused a greater concentration (about 60 mg per g) even though 30 percent of the polyol dose was lost in the urine.

Sorbitol has been administered as an energy source in parenteral nutrition to adult beagle dogs (Meng, 1974). Infusion rates were 0.42 to 0.7 g per kg per hour with up to 16.75 g per kg per day during a 40-day period. A serum sorbitol content of 21 mg per dl was recorded in one dog when urinary sorbitol levels were
at their highest. Blood glucose levels were generally within normal limits and sorbitol retention, measured by urinary loss, was approximately 90 percent. A diuretic effect was not observed in this study; however, urinary sorbitol loss appeared to be increased by other nutrients, particularly by coadministration of amino acids. Sorbitol administration was associated with negative nitrogen balance in dogs receiving total parenteral nutrition and in dogs consuming carbohydrate-free or carbohydrate-fat-free diets in conjunction with parenteral sorbitol. Serum glutamic-pyruvic transaminase and alkaline phosphatase were elevated in a reversible manner. No histopathological changes were attributable to the infusion of sorbitol. It is logical to conclude that sorbitol was utilized as an energy source.

2. Feeding studies.

After reviewing the toxicological data available, the Select Committee on GRAS Substances (1972) concluded that no evidence existed to show that sorbitol as a food ingredient constituted a hazard to the general public when it was used at then current levels or at a level that might reasonably be expected in the future. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (1964, 1974) were in accord with this finding until recently when further toxicological work was suggested (Joint FAO/WHO Expert Committee on Food Additives, 1978). The earlier studies reviewed by these Committees are summarized in Table 3. Additional unpublished reports (Gongwer and Hubben, 1969; Heywood et al., 1978; Hummler, 1978; Hunter et al., 1978; Palmer and Bottomley, 1978; Palmer et al., 1978) are presented here in more detail.

a. Two-year feeding study in rats. Sorbitol was fed to Sprague-Dawley rats at dietary levels of 0, 1, 5, and 10 percent; the two highest levels were supplemented with casein to maintain a 25 percent dietary protein level (Gongwer and Hubben, 1969). Vitamin supplements were added to these two diets after the first 5 months. The study involved a total of 192 rats and included equal numbers of males and females. Data were recorded on appearance, laxation, body weight gain, survival, gross examination of tissues at necropsy, and organ weight of the adrenal glands, gonads, heart, kidneys, liver, and spleen. At weeks 63 and 98, blood glucose levels and qualitative urinary sugar were measured. Groups of eight male and eight female rats representing each of the diets were observed for food consumption, water consumption, urine output, and urine composition (for specific gravity, pH, and qualitative sugar, albumin, and acetone).

Diarrhea occurred during the first 2 months in a few rats at the 10 percent dietary level (12 g per kg per day). Male rats experienced a reduced rate of weight gain after 1 year at the 10 percent level (5 g per kg per day) and showed lower weights than controls at 65 and 104 weeks. Water consumption and urine output were slightly increased by dietary sorbitol but no clear dosage relationship appeared.
TABLE 3. Toxicological studies of sorbitol reviewed by the Joint FAO/WHO Expert Committee on Food Additives (1964, 1974) and the Select Committee on GRAS Substances (1972).

<table>
<thead>
<tr>
<th>Species</th>
<th>Route and dose</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute toxicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>Oral</td>
<td>$\text{LD}_{50}$: male, 23,200; female, 25,700 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\text{LD}_{50}$: male, 17,500; female, 15,900 mg/kg</td>
</tr>
<tr>
<td>Rat</td>
<td>Oral</td>
<td>$\text{LD}_{50}$: male, 7,100; female, 7,300 mg/kg</td>
</tr>
<tr>
<td></td>
<td>iv</td>
<td>$\text{LD}_{100}$: 26,000</td>
</tr>
<tr>
<td>Rat, male</td>
<td>Oral</td>
<td>No toxic effects.</td>
</tr>
<tr>
<td>Man (adult)</td>
<td>Oral, 670 mg/kg, divided dose</td>
<td>No laxative effect; gas in bowel.</td>
</tr>
<tr>
<td>Man (86 adults)</td>
<td>Oral, 417 mg/kg, 25 g in 2 doses</td>
<td>Diarrheal stools in infants.</td>
</tr>
<tr>
<td>Man (infant, 20–35 mo)</td>
<td>Oral, 9.3 g</td>
<td></td>
</tr>
<tr>
<td>(child, 5–6 yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-term studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat, male</td>
<td>Diet (5%), 3 months</td>
<td>No toxic effects.</td>
</tr>
<tr>
<td>Rat, female</td>
<td>Stomach tube, 0.675–3.0 g/kg, 3 times daily, 5 doses</td>
<td>Mild dose-dependent &quot;irritation&quot; of stomach and duodenum.</td>
</tr>
<tr>
<td>Rabbit</td>
<td>iv, 11 days with amino acids 2.8 g/kg/day</td>
<td>No histopathological changes.</td>
</tr>
<tr>
<td>Dog</td>
<td>iv, 1.25 g/kg</td>
<td>Diuretic effect at 1 h.</td>
</tr>
<tr>
<td>Dog: male, female</td>
<td>Stomach tube, 0.675 &amp; 1.35 g/kg, 3 times daily, 9 doses</td>
<td>Stomach hyperemic at highest dose.</td>
</tr>
<tr>
<td>Monkey (Rhesus)</td>
<td>Diet, 3 months, 8 g/kg/day</td>
<td>No toxic effects.</td>
</tr>
<tr>
<td>Man (adult)</td>
<td>Oral, 167 mg/kg/day, 10 g/dose, 1 month</td>
<td>No toxic effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laxative effect above 50 g as a single oral dose.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Details</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Long-term studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>Diet (5%), 3 generations</td>
<td>No toxic effects, no gross or histologic abnormalities.</td>
</tr>
<tr>
<td>Rat (Wistar)</td>
<td>Diet (10-15%), 17 months per generation, 4 generations</td>
<td>No toxic effects, slight initial diarrhea, no gross or histologic abnormalities.</td>
</tr>
<tr>
<td>Rat</td>
<td>Diet (16%), 19 months</td>
<td>Hypercalcemic, bladder concretions, thickening of skeleton, citrate excretion.</td>
</tr>
<tr>
<td>Host-mediated assay, mouse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saccharomyces cerevisiae D-3</td>
<td>0.030-5 g/kg</td>
<td>Slight increase in mitotic recombination frequency for <em>S. cerevisiae</em>.</td>
</tr>
<tr>
<td>Salmonella typhimurium G-46, TA1530</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant lethal gene test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>0.030-5 g/kg</td>
<td>Results negative.</td>
</tr>
<tr>
<td>Cytogenetic assay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat bone marrow metaphase</td>
<td>0.030-5 g/kg</td>
<td>Results negative.</td>
</tr>
<tr>
<td>chromosomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human embryonic lung cells</td>
<td>10-1000 µg/ml, <em>in vitro</em></td>
<td>Moderate response scored at anaphase.</td>
</tr>
<tr>
<td>(WI-38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teratogenicity test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mice, rats</td>
<td>1600 mg/kg/day, days 6-15 of gestation</td>
<td>No teratogenic response.</td>
</tr>
<tr>
<td>Hamsters</td>
<td>1200 mg/kg/day, days 6-10 of gestation</td>
<td>No teratogenic response.</td>
</tr>
</tbody>
</table>

*aTreon, 1963; *bCarr and Forman, 1939; *cPeters and Lock, 1958; *dGrybowski, 1966; *eEllis and Krantz, 1941, *fStaples et al., 1967; *gGriem and Lang, 1960; *hLeimdorfer, 1954; *iEllis et al., 1943; *jLe Breton, 1956; *kFournier et al., 1967; *lStanford Research Institute, 1972; *mFood and Drug Research Laboratories, Inc., 1972.
Tissues of 10 male and 10 female animals randomly selected from the group consuming the diet of 10 percent sorbitol and from the controls were examined histologically. The investigators concluded that tissues and organs showed no greater frequency or degree of abnormalities in the 10 percent group than in the control rats. However, certain findings detract from this study. The incidence of chronic pyelonephritis and the adverse cystic findings in the adrenals, which may have been associated with pathological change in the kidneys, were considered abnormally high in all groups (Gongwer and Hubben, 1969). Such findings make the interpretation of the results difficult; however, the investigators considered all observed effects as neither deleterious nor dosage or sorbitol related. Significant changes were seen in the kidneys and adrenals in the group fed 10 percent sorbitol and in the control group; tumors, mostly related to organs of the reproductive systems and related endocrine glands, had a greater incidence among female than male rats of both groups. While not noted as significant, the frequency of calcification in the aorta and enlarged hyperplastic parathyroid glands tended to be greater in male rats on the sorbitol diet than treated females and controls of both sexes. Further, the incidence of chromophobe cell hyperplasia in the pituitary was 20 percent (6 of 30) in the treatment groups as compared with 3 percent (1 of 35) in the control group; the investigators did not comment on the possible statistical significance of these observations.

b. Sorbitol feeding in toxicological study of xylitol. Studies, designed primarily to test the safety of xylitol, included groups of rats, rabbits, and dogs fed sorbitol or sucrose at a level of 20 percent in the diet. Three trials involved Sprague-Dawley rats (CD strain): (1) long-term tumorigenicity and toxicity studies (Hunter et al., 1978), (2) a "modified" teratology study (Palmer and Bottomley, 1978), and (3) reproduction study of three generations (Palmer et al., 1978). A teratology test was done using rabbits (Hummler, 1978), and beagle dogs were studied in a 2-year toxicity study (Heywood et al., 1978). Summary reports of these studies were available for review but the data have not been published in the scientific literature.

(1) The 2-year study in rats by Hunter et al. (1978) showed the following reactions for both sexes related to sorbitol treatment: enlargement of the cecum, lower bodyweight gain, higher water intakes and excretion of larger volumes of dilute urine during the initial 78 weeks, impaired food efficiency, lower absolute thyroid weights at the conclusion of the trial, and a significantly greater incidence of adrenal medullary hyperplasia. Females, but not males, had higher insulin levels on the sorbitol diet at weeks 26 and 52. Many of the effects noted for sorbitol were also noted in animals given xylitol or, in some instances, sucrose. Lower insulin levels were recorded at week 78 for females receiving 20 percent xylitol; an increase in the incidence of adrenal medullary pheochromocytomas among male rats receiving 20 percent xylitol was not seen among the control, 20 percent sucrose, or 20 percent sorbitol groups (Table 4) (Hunter et al., 1978).

<table>
<thead>
<tr>
<th>Diet</th>
<th>Adrenal medullary hyperplasia</th>
<th>Adrenal medullary pheochromocytomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male</td>
<td>female</td>
</tr>
<tr>
<td>Control</td>
<td>5/60</td>
<td>1/62</td>
</tr>
<tr>
<td>2% Xylitol</td>
<td>6/60</td>
<td>1/63</td>
</tr>
<tr>
<td>5% Xylitol</td>
<td>8/59</td>
<td>8/61*</td>
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<tr>
<td>10% Xylitol</td>
<td>12/62*</td>
<td>7/64*</td>
</tr>
<tr>
<td>20% Xylitol</td>
<td>16/61*</td>
<td>11/65*</td>
</tr>
<tr>
<td>20% Sorbitol</td>
<td>15/62*</td>
<td>8/64*</td>
</tr>
<tr>
<td>20% Sucrose</td>
<td>4/57</td>
<td>2/62</td>
</tr>
</tbody>
</table>

*Level was of statistical significance (Hunter et al., 1978).
(2) In the modified teratology test by Palmer and Bottomley (1978), nonpregnant female rats were fed increasing dietary levels of the test material for a 5-week period until the final concentrations (0, 2, 5, 10, and 20 percent xylitol, 20 percent sucrose, and 20 percent sorbitol) were achieved prior to mating with untreated males. While the overall pregnancy rate (average = 55.9 percent, range = 31.3 to 77.4 percent) was low, the only effect noted in any group was slightly reduced food intake in the sorbitol-fed group. Embryonic and fetal development were not adversely affected by the substances being tested (Palmer and Bottomley, 1978).

(3) In a three-generation study in rats, 5 percent sorbitol was fed to both sexes of the F₀ generation and to nursing dams after birth of the second litters (F₁B, F₂B, F₃B) in subsequent generations (Palmer et al., 1978). A dietary level of 20 percent sorbitol was achieved by gradual increase from 5 percent in the F₁B and F₂B generations. Reductions in food consumption and body weight gain were detected prior to reaching the 20 percent level in the diet. Rats on this diet showed, within the normal range, a consistent tendency toward prolonged duration of gestation. This effect occurred to a lesser extent in the 20 percent xylitol group. Sorbitol-fed groups showed increased cecal weights (F₂B adults), lower total and viable litter size at birth with a higher mean pup weight, and, in first litters, an increased perinatal mortality at day 4 postpartum. Values for litter size and mean pup weight at weaning were not significantly different from controls; however, lower pup weight gain during the second half of the lactation periods, particularly in the F₂B generations, resulted in lower weaning weight (21 days postpartum) of the F₃B offspring. Selection was made from among the F₃B young for detailed examination and two observations, both related to sorbitol, were included in the summary of the study without interpretation of their significance:

"(a) The absence of (or reduced numbers of) small foci of mononuclear cells in hepatic sinusoids or portal tracts in 1/10 males with 20% Xylitol and 2/10 males, 1/10 females with 20% Sorbitol. (b) Ill-defined thymic structure (macroscopic) associated with cortical lymphocyte depletion in 1/10 males and 1/10 females from the 20% Sorbitol group: both animals were derived from the same litter and showed other histopathological changes" (Palmer et al., 1978).

(4) Pregnant rabbits fed sorbitol (6.8 to 7.8 g per kg body weight) from the 7th to the 19th day of gestation showed no reproductive impairment; measured parameters included litter size, fetal weight, and resorption rate (Hummler, 1978).

(5) A group of pure-bred beagle dogs (eight males and eight females) fed 20 percent sorbitol for 2 years gained significantly more weight than controls but showed only a
slightly greater food efficiency (weeks 0 to 26) than dogs in
groups fed 2, 5, 10, and 20 percent xylitol or 20 percent sucrose
(Heywood et al., 1978). Relative organ weights were comparable
or slightly lower than controls after 2 years. During weeks 35
to 58, the water consumption of males consuming sorbitol was
increased and, after week 49, the total serum protein levels of
both sexes were slightly elevated. No abnormalities were attrib-
uted to sorbitol treatment (Heywood et al., 1978).

c. Summary of feeding studies. The rat is the only
experimental animal that has been used in long-term feeding
studies of sorbitol. These included multigeneration studies and
feeding at several dietary levels from 1 to 20 percent. Other
species fed sorbitol for shorter periods were the dog and monkey
and, in teratology tests, the rabbit. The rat studies gave inco-
sistent findings, e.g., effects in various glandular tissues and
the dietary level at which certain effects occurred. The composi-
tion of the basal diet, the strain of rats, and the age of the
rat when sorbitol was introduced to the diet varied among studies.
There were frequent indications that rats were stressed as evi-
denced by food avoidance and reduced weight gain, water and min-
eral imbalance, and cecal enlargement. Evidence of these effects
was seen even in relatively short-term studies (5 to 8 weeks) when
sorbitol was fed at 10 percent or higher dietary levels to differ-
ent strains of young rats (Karle, 1977; Mühlemann et al., 1970;
Shaw, 1976). Growth depression occurred in the short-term study
of Ellis and Krantz (1941) when 20- to 28-day-old male rats were
fed 5 percent sorbitol (replacing glucose in a 40-percent glucose
basal diet), but 5 percent sorbitol did not depress growth and did
not induce adverse effects in a multigeneration study with a
laboratory chow as the basal diet (Ellis et al., 1943). Gongwer
and Hubben (1960) noted growth depression at 2 months in male
Sprague-Dawley rats fed 10 percent sorbitol but not in rats fed 1
or 5 percent sorbitol; diarrhea and soft stools were evident
during the first few months in rats fed a diet with 10 percent
sorbitol and to a lesser degree in rats fed a 5-percent sorbitol
diet. During the initial 3-week feeding period, the 10-percent
sorbitol diet gave an average sorbitol dose in excess of 12 g per
kg per day.

A slight initial growth depression but no gross or histo-
logical abnormalities were seen by Le Breton (1956) in a four-
generation study of Wistar rats fed up to 15 percent sorbitol
(about 7.50 g per kg per day for an adult) for 17 months per gener-
ation. In contrast to this and later studies, Fournier et al.
(1967) produced hypercalcemia, bladder concretions, thickening of
the skeleton, and elevated excretion of citrate in rats fed a diet
containing 16 percent sorbitol for 19 months. Signs of hypercal-
cemia began to appear after 3 months of feeding sorbitol. Exten-
sive tissue calcification was not seen in rats fed 20 percent
sorbitol by Hunter et al. (1978) or at 10 percent by Gongwer and
Hubben (1969). These several feeding studies raise a number of
unanswered questions warranting additional studies into the underlying mechanisms, particularly because the effects are not seen consistently. These include serum calcium elevation and tissue calcification, altered weights and possibly altered function of thyroid and parathyroid glands, adrenal medullary hyperplasia, and possible pituitary chromophobe cell hyperplasia.

Many of the animal feeding studies have not been published in the scientific literature. It would be helpful to have the protocols for the long-term rat feeding studies examined and possibly repeated and extended by other investigators to other species including subhuman primates. The potentially adverse effects observed in rats occurred at feeding levels that provided sorbitol intakes exceeding the rate, 0.25 g per kg body weight per hour, at which human beings can utilize sorbitol metabolically. The evidence available from animal feeding studies does not suggest that human beings will experience adverse health effects from ingesting sorbitol as currently used as a food ingredient.

3. Special studies.

Tests in Drosophila melanogaster for the induction of somatic mutations, sex-linked recessive lethals, and chromosome loss indicated that sorbitol was nonmutagenic (Abbott and Bowman, 1976). When investigated for toxic and teratogenic effects to the developing chicken embryo, sorbitol was not teratogenic even at relatively high dosages, 40 mg per egg (Hwang and Connors, 1974). Sorbitol was embryotoxic at all levels when administered at 96 hours of incubation except at 1.0 and 10.0 mg per egg via the yolk; probit analysis revealed no dose-dependent relationship. Sorbitol was not embryotoxic when administered to the embryo at the preincubation stage at a dosage level at or below 25 mg per egg. The evidence in these studies and those summarized in Table 3 supports the conclusion that sorbitol is neither mutagenic nor teratogenic when evaluated with accepted microbial and animal test protocols.

B. HUMAN STUDIES

1. Parenteral administration.

Froesch and Jakob (1974) state that the administration of sorbitol and xylitol for parenteral nutrition is without advantage and poses considerable danger of lactic acidosis if large amounts of fructose, sorbitol, or xylitol are given. Förster (1974), however, contends that under certain conditions of impaired glucose tolerance -- diabetes mellitus, the postoperative state, or severe burns -- fructose, sorbitol, and xylitol may be better suited for intravenous therapy than glucose. Cahill (1972) expressed doubt that any substitute for glucose will be found that can be given parenterally in amounts sufficient to meet caloric requirements and for which adequate metabolic pathways exist within the human body.
Fürster (1974) administered intravenously 1.5 g per kg of sorbitol to healthy human volunteers within a period of 20 minutes. Blood glucose levels showed no significant rise but blood lactate levels rose significantly, comparable to those after a dose of glucose or fructose. The lactate-pyruvate ratio increased minimally to 16 from a control value of 12. In contrast, the ability to tolerate and utilize parenterally administered sorbitol is limited in certain patients. For example, Batstone et al. (1977) described the production of reversible acidosis in a 70-year-old male patient after a series of short-term infusions of a mixture of sorbitol, ethanol, and amino acids. The acidosis was associated with deterioration of hepatic and renal function; blood pyruvate concentration was 0.10 and the blood lactate more than 10 mmol per l in contrast to the normal range of lactic acid concentrations of 0.6 to 1.8 mmol per l (Scully, 1978). The lactate-pyruvate ratio reached 105.

Side-effects limit the amount of a single carbohydrate, such as sorbitol, that can be given to meet glucose and caloric requirements for a sustained period of time (Bässeler and Schultis, 1975; Kearney, 1976). The adverse effects of parenterally administered sorbitol are characteristic of those observed for other non-glucose carbohydrates and are very dependent on the rate, duration, and total dose. The effects include, to varying degrees, increases in the blood lactate leading to lactic acidosis; increases in serum uric acid, transaminases, and bilirubin; and in the case of xylitol, the possible deposition of oxalate crystals in the kidney (LSRO, 1978).

Bickel et al. (1973) observed no adverse effects in healthy volunteers after infusion of sorbitol at rates between 0.25 and 0.5 g per kg per hour for up to 6 hours. Renal loss exceeded 11 percent of the dose at the 0.5 g per kg per hour rate. An infusion rate of 0.75 g per kg per hour appeared to exceed the ability of the body to maintain a steady state condition, and 31 percent of sorbitol administered was excreted. Kearney (1976) suggests the renal threshold for sorbitol is exceeded if sorbitol is administered parenterally to humans at a rate exceeding 0.6 g per minute. Matzkies (1975) found that intravenous administration of sorbitol at a rate of 0.5 g per kg per hour for 9 hours caused nausea and vomiting in normal subjects; sorbitol blood concentration rose for 0 to 44.7 mg per dl after 3 hours and to 75.9 mg per dl after 9 hours. Infusion rates of 0.25, 0.375, and 0.5 g per kg per hour resulted in excretion of 29.4, 35.2, and 46.7 mg per kg per hour of sorbitol and biological half-lives of 0.59, 0.43, and 0.40 hour, respectively; the blood level of sorbitol was maintained at about 20 mg per dl when sorbitol was infused at 0.25 g per kg per hour for 12 hours. Bickel and Halmágyi (1974) noted the maximum utilization capabilities for glucose and fructose were 3 to 4 times as high as that for sorbitol. They postulated that a mixture of carbohydrates may be advantageous for parenteral use postoperatively because caloric requirements cannot be met under metabolic limitations imposed on infusion rates of individual carbohydrates.
The normal 24-hour urinary excretion of hexitols by diabetes mellitus patients not consuming hexitols was found to be five times that of control subjects (Heaf and Galton, 1975). The relative proportion of sorbitol, galactitol, and mannitol in the urine was not determined in this study. A preliminary report of Gabbay (1974) indicates a large amount of mannitol can be excreted by diabetes mellitus patients while streptozotocin-diabetic rats excrete sorbitol but not mannitol. Increases in blood sorbitol content may result in increased sorbitol excretion due to a low renal threshold.

2. Oral administration.

Much of the research relevant to human ingestion of sorbitol has been directed toward two areas and has relied primarily on experimental animal models: (a) characterizing its metabolism in normal and diabetic individuals and (b) evaluating its cariogenicity and effect on the cariogenicity of other dietary components.

For human beings, a substantial objection to ingesting large quantities of sorbitol is its incomplete absorption. While normal and diabetic subjects eliminated little sorbitol in the urine and none was detected in the feces after oral administration, antibiotics caused up to 10 percent of ingested sorbitol to be eliminated in the feces (Adcock and Gray, 1957). This suggests that a significant fraction, perhaps 10 percent, passes through the small intestine unchanged and undergoes fermentation by bacterial action in the colon. This would be expected to cause diarrhea in a manner analogous to that seen in the lactase-deficient individual after the ingestion of milk (Johnson et al., 1974). The usual amount of sorbitol ingested in foods represents a different physiological situation than the ingestion of test doses of crystalline or aqueous sorbitol that produce laxation in human beings (Ellis and Krantz, 1941; Macdonald et al., 1978). The humectant and osmotic effects of sorbitol may also contribute to laxation (Peters and Lock, 1958). The maturity of the gastrointestinal tract as a factor was amply shown in infants (Grybowska, 1966) and in experimental animals, even when sorbitol was fed as a dietary component (Le Breton, 1956; Hunter et al., 1978). Individuals might reasonably be anticipated to avoid ingesting amounts of sorbitol in their diets which are causative of laxation. However, insufficient data are available concerning the laxative effect of sorbitol ingested as a food ingredient to assess the extent to which laxation plays a role in limiting the total sorbitol intake of human beings.

a. Diabetes mellitus. Exogenous sorbitol, as well as xylitol and fructose, continues to be of interest to dietologists in their search for a nutritive substitute for glucose and sucrose that does not lead to marked hyperglycemia and thus might be useful in the metabolic stabilization of the unstable diabetic patient (Brunzell, 1978; Talbot, 1978). The initial
steps in the metabolism of sorbitol in liver, its uptake by liver cells, and its conversion to glucose are independent of insulin, but the subsequent utilization of glucose by the muscle and adipose tissues is influenced by insulin (Winegrad, et al., 1972).

Studies in experimental animals illustrate differences in the metabolic responses of normal and diabetic animals to sorbitol administration (Froesch et al., 1971; Keller and Froesch, 1971). In a normal animal, a hyperglycemic response to the parenteral administration of sorbitol, xylitol, or fructose is attenuated by insulin, and this effect on the liver is balanced by hormones antagonistic to insulin. For example, the livers of diabetic rats synthesized more glycogen than the livers of normal rats after a parenteral dose of sorbitol, fructose, or xylitol was administered with insulin; liver glycogen synthesis in streptozotocin-diabetic rats receiving insulin was greater from sorbitol than from either xylitol or fructose (Froesch et al., 1971). The percentage (11 to 18 percent) of a parenterally administered dose expired as CO₂ differed little in diabetic rats receiving radiolabeled glucose, fructose, xylitol, or sorbitol (Keller and Froesch, 1971). On the other hand, after a 24-hour fast, normal rats expired approximately 20 percent of a sorbitol dose as CO₂ compared with 35 percent of the other substrates. The percentage of the administered radiolabel excreted in the urine was also greater within 6 hours after sorbitol (24 percent, largely as glucose) as compared with fructose (7 percent) or glucose (3 percent) administration.

No increase was observed in the blood glucose levels or respiratory quotient of 13 mild or moderately severe diabetic patients ingesting 50 g of sorbitol; however, a 50-g dose of sorbitol elevated the respiratory quotient of normal individuals (Ellis and Krantz, 1941; 1943). In all cases, blood glucose levels rose only minimally after sorbitol ingestion.

After a 12-hour fast, nine healthy male students received 0.25, 0.5, 0.75, or 1.0 g glucose, sucrose, fructose, or sorbitol per kg body weight by mouth (1.0 g sorbitol was not tested because it resulted in diarrhea) (Macdonald et al., 1978). Venipuncture was performed at 15, 30, 60, and 90 minutes. Only glucose ingestion decreased serum lactate concentration. Serum uric acid levels increased after fructose and sucrose but not after sorbitol or glucose ingestion. Minimal insulin response was noted after fructose ingestion. Sorbitol ingestion was associated with a small increase in serum insulin and low serum fructose levels. Of the carbohydrates tested, only sorbitol did not cause serum glucose levels to increase at any of the dosage levels tested.

Few studies have investigated the metabolic response of human beings ingesting mixed meals in which a substantial portion of the simple carbohydrates was replaced by sorbitol. Puls and Keup (1973) fed one of the following two test meals to six normal male subjects who had been fasted overnight:
(a) 2 rolls (65 g starch)  
  butter (37.5 g)  
  40 g jam (24 g sucrose)  

(b) 2 rolls (65 g starch)  
  butter (37.5 g)  
  40 g jam (22 g sorbitol)

The responses of blood glucose and free fatty acid levels were similar after both meals; blood glucose rose slightly above baseline and free fatty acid levels decreased after 60 minutes. Insulin (immunologically reacting) levels increased more rapidly and reached greater concentrations after the sucrose jam; however, blood glucose levels for the two groups were similar over a period of 3 hours.

Vaaler et al. (1978) investigated the blood glucose response of nine juvenile diabetic subjects to two similar test meals:

(a) white bread (90 g)  
  butter (9 g)  
  100 g jam (0.02 g saccharin,  
  18 g sucrose)  

(b) white bread (90 g)  
  butter (9 g)  
  100 g jam (0.02 g saccharin,  
  18 g sorbitol)

The meals were fed to subjects who had fasted overnight and had not received insulin prior to the test. No statistically significant differences were observed in the postprandial rise in blood glucose.

Arvidsson Lenner (1976) studied the blood and urine glucose levels of nine diabetic and three normal adult subjects, ages 60 to 75, who consumed test meals in which sucrose was partially replaced by fructose or sorbitol. No significant differences were noted, and the investigator concluded that neither fructose nor sorbitol offered advantages over sucrose in this regard for well-regulated adult diabetes mellitus patients. An ad hoc group convened at FASEB to consider the need for special food and sugar substitutes by individuals with diabetes mellitus came to essentially the same conclusion: "...sorbitol offers few advantages as a sugar substitute for use by diabetic patients because of its relatively greater potential to induce diarrhea and its low level of sweetness compared with fructose or xylitol. It offers no advantage in controlling caloric intake" (Talbot, 1978). There are no reports of long-term use of sorbitol as a sucrose substitute in mixed meals for patients with diabetes mellitus.

Duane (1978) developed a model for cholesterol cholelithiasis by feeding sorbitol to nine healthy male subjects (age 22 to 61 yr) for periods of 2 to 3 weeks. Sorbitol was mixed uniformly with each meal and with between meal snacks; the dose was adjusted during the first 2 to 4 days so that no subject had diarrhea (defined as one or more watery stools per day or an increase of more than one daily bowel movement compared to a 2-week control period). A daily intake of 15 to 60 g of sorbitol reduced the mean small bowel transit time a minimum of 42 minutes from a value of 86 minutes. The changes in bile metabolism approximated those
found in many patients with cholesterol gallstone disease. The relative cholesterol content increased from 6.99 to 7.81 molar percent and the total bile acid pool (cholic, chenodeoxycholic, and deoxycholic acids) was reduced in all subjects an average of 27 percent. The reduced pool size was attributed to a combination of decreased synthesis and increased fractional turnover. Duane (1978) suggested that the ingestion of other nonabsorbable carbohydrates such as raffinose, stachyose, verbascose, or, in some cases, lactose, may have practical implications for a population with a high prevalence of cholesterol gallstone disease.

b. Dental caries. Assessment of the cariogenicity of sorbitol involves evaluation of its ability to initiate a lesion and to support progression of the carious process. Plaque formation by Streptococcus mutans and subsequent acid dissolution of enamel mediated by fermentation of available carbohydrate sources have been identified through animal and clinical studies as integral components of cariogenicity (Kimura and Carr, 1976; LSRO, 1978). The results of cariogenicity studies are difficult to compare because subjective judgments are involved in quantitation of these parameters. In addition, experimental conditions, diet composition, and the experimental animal studied vary between laboratories.

Short-term animal feeding studies relevant to the cariogenic properties of sorbitol have been done in rats (Karle, 1977; Mühlemann et al., 1970; Shaw, 1976; Shaw and Griffiths, 1960), hamsters (Frostell et al., 1967), and monkeys (Cornick and Bowen, 1972). When fed as a component of the diet, sorbitol's cariogenicity varied. One preliminary report (Navia et al., 1974) compared sucrose, fructose, and sorbitol fed to rats at a level of 5 percent in a cornstarch diet and showed no differences in buccal or sulcal caries scores. However, in other studies, the cariogenicity of sorbitol was generally less than that of sucrose, dextrin, cornstarch, or fructose fed under similar conditions. Osborne-Mendel rats fed a control diet containing 64 percent wheat flour from age 22 days through age 55 days had a low incidence of caries (Mühlemann et al., 1970). This incidence was not changed in groups of rats fed 10, 20, and 30 percent xylitol, which was substituted for flour. However, sorbitol increased the average number of dentinal fissure carious lesions when fed at 10, 20, and 30 percent of the diet; the increase was slight and not dose dependent. Increased water intake was associated with diarrhea in animals receiving either sorbitol or xylitol at 20 and 30 percent of their diets.

In the Harvard caries-prone strain of rats, mixtures of sucrose or dextrin with 20 to 67 percent sorbitol or mannitol caused a lower rate of caries initiation and progression than was observed when sucrose or dextrin was fed in a semipurified diet (Shaw and Griffiths, 1960). When fed for 60 days in a 57 or 62 percent corn starch diet to a mutant albino caries-prone
strain, sorbitol at 5 or 10 percent of the diet was not more cariogenic than starch (Shaw, 1976). In this experiment, growth rates as compared to controls tended to be less for both sexes at both levels of sorbitol, but the reduced rate was statistically significant only in females receiving 10 percent sorbitol.

Karle (1977) demonstrated that xylitol and sorbitol were less cariogenic than fructose and sucrose when fed for 6 to 8 weeks with glucose in the diets of male Sprague-Dawley rats. Feeding xylitol or sorbitol at dietary levels increased from 10 to 30 percent over a period of 6 to 8 weeks led to lower rate of growth, pronounced dilation of the cecum, and to changes in the mucous membranes of the cecum and colon, particularly in the case of sorbitol.

Cornick and Bowen (1972) observed two, small carious lesions in one of eight monkeys (Macaca irus) that were fed diets containing 1 g of sorbitol daily for periods of up to 2 years, while all the control animals (receiving sucrose diets) developed severe caries. The capacity of the plaque to ferment sorbitol was not altered by feeding sorbitol, and the investigators concluded that, even though most strains of extracellular polysaccharide-producing streptococci resembling S. mutans are capable of fermenting sorbitol to pH values of 4.5, long-term consumption of sorbitol would not induce a plaque capable of rapid fermentation of sorbitol.

Mäkinen et al. (1978) have suggested that the function of the exocrine glands involved in digestion may be affected by the principal carbohydrate component of the diet and that this may affect indirectly the development of plaque and acid production by S. mutans. They studied the effects of xylitol, sucrose, and sorbitol on monkeys by including the test compound in the drinking water (5 percent, w/v) and as part of a mixed diet at a level providing a total intake of 15 to 20 g per day for 3 days. The animals consuming xylitol had slightly loose stools. The lactoperoxidase concentration in parotid saliva collected by pilocarpine stimulation from M. mulatta was greater after xylitol feeding than after sucrose feeding. A comparison of xylitol and sorbitol in M. fascicularis suggested that lactoperoxidase concentration was affected similarly by both polyols. Sucrose and sorbitol were not compared in the same species. However, the investigators concluded that the consumption of xylitol may have stimulated selectively the synthesis in the salivary glands or accumulation in acinar cells of (glyco)proteins because the concentrations of phosphate, calcium, and SCN ions were not affected by xylitol to the same extent as the concentration of amylase, lactoperoxidase, and total protein. Gastric intubation of 2.5 g of xylitol had no effect on lactoperoxidase concentration. Other studies showed xylitol increased the lactoperoxidase concentration in human saliva and the activity of this enzyme apparently correlated with a reduction in the incidence of dental caries in the Turku studies (Mäkinen et al., 1976; Scheinin et al., 1975). Further research
is needed on sorbitol and polyols in general to establish whether or not polyols affect the function of the exocrine glands, to elucidate the mechanism by which such functional changes occur, and to assess the nature of long-term effects on health of these changes.

Koulourides et al. (1976) submitted samples of bovine enamel surfaces to simulated cariogenic conditions in the human mouth and assessed the extent of experimental cariogenesis using a test for microhardness. Of the simple carbohydrates tested, lactose, mannitol, melibiose, and sorbitol were significantly less cariogenic than sucrose while xylose and xylitol were noncariogenic by this technique.

Most of the studies related to the cariogenicity of sorbitol in human beings have included sorbitol in candies and gums or simply as a solution used as a mouthwash rather than as a component of the diet. The studies have focused on dissolution of enamel as well as adaptive changes in the oral microflora and the pH of dental plaque. Guggenheim (1968) demonstrated that certain strains of streptococci isolated from children fermented sorbitol and mannitol and were cariogenic in rats. However, the rate of fermentation and the ability to lower plaque pH value appears limited in studies involving short-term exposures of the oral microflora to sorbitol (Graf, 1970; Mühlemann, 1969). After rinsing a subject's mouth with a 10 percent solution of sorbitol or sucrose, Mühlemann (1969) measured the pH within the dental plaque. The pH remained between pH 6 and 7 in the case of sorbitol, but decreased to pH 4 within 40 minutes after sucrose exposure. In one experiment, a pH of about 6 occurred when sorbitol gum was chewed in a series immediately after the plaque was made pH 4. Clark et al. (1961) reported no significant change in the amount of acid produced from sorbitol by samples of saliva from six subjects who sucked three sorbitol tablets daily after meals for 4 weeks. Gallagher and Pearce (1977) pointed out that the decalcification may begin at about pH 5.5 and cautioned that Frostell (1965) had demonstrated an adaptation of oral flora in dental plaque of eight subjects who chewed sorbitol tablets daily for 2 to 6 months. Longer term studies in human beings tend to support this view. Plaque isolated from individuals who consumed xylitol and sorbitol in their diets for 3.2 to 4.5 years produced a pH of 3.9 to 5.5 during incubation with sorbitol (Mäkinen and Virtanen, 1978). However, a human population that regularly consumes sorbitol-containing foods such as jams and jellies, baked goods, frozen dairy desserts, or other food products in addition to sorbitol-containing gums and candies has not been identified and studied to establish whether or not sorbitol significantly alters the carious process.

Carefully controlled studies in which children chewed sorbitol-containing gums have been designed primarily to study the effect on caries development of various chewing gum ingredients
such as dicalcium phosphate (Finn and Jamison, 1967; Richardson et al., 1972) and sodium trimetaphosphate (Finn et al., 1978) rather than to evaluate the cariogenicity of sorbitol per se. The results of Möller (1977) indicate a depression in the caries progression rate in children who, over a 2-year period, chewed gum made with sorbitol and calcium phosphate. In the study of Finn et al. (1978), children who chewed a polyol-sweetened gum (containing 50 to 70 percent sorbitol and mannitol) or those who did not chew gum had greater caries increments over a 30-month period than children who chewed the polyol-sweetened gum to which sodium trimetaphosphate had been added. The results of these four studies do not provide definitive data on the effect of sorbitol on caries development.

In a 2-week study, three groups of school children, aged 14 to 16, either chewed gum and tablets containing xylitol and sorbitol (26 children), received no sweetened gum and candy (8 children), or consumed sucrose-sweetened chewing gum and other sweet items (21 children) (Harjola and Liesmaa, 1978). The three groups were scored on the basis of visible plaque index (VPI), gingival bleeding index (GBI), and lactobacillus index before and after the test period. The VPI and GBI scores of the group consuming no sweets and the group given the xylitol-sorbitol mixture were substantially reduced; the VPI and GBI were unchanged in the sucrose groups. The lactobacillus index showed high intra-group variability but the value decreased in the no-sweet and xylitol-sorbitol groups.

In summary, the weight of evidence from animal studies suggests that sorbitol is less cariogenic than sucrose, fructose, glucose, and dextrin. It is logical to assume that sorbitol may have similar relative cariogenic properites in human beings.
V. CONCLUSIONS

Sorbitol is a natural constituent of many fruits and a normal metabolite found at low levels in animal tissues. It is added to a wide variety of processed foods to produce several technical effects. Processed foods may contribute substantial quantities of sorbitol to the individual diet.

Available food consumption data are inadequate to allow estimation of the actual quantities of added sorbitol ingested by persons preferentially selecting sorbitol-containing products.

Ingested sorbitol is absorbed through the intestinal wall by passive diffusion. There is no evidence that a specific transport system for sorbitol exists in any cell type.

There are insufficient data available to assess accurately the effects of dietary composition on the rate and extent of sorbitol absorption, its laxative effects, and caloric value. The caloric value of sorbitol is considered similar to that of other carbohydrates in the diet; however, it has not been determined precisely in experimental animal studies.

Sorbitol affects the absorption and/or retention of several nutrients including vitamin B₁₂, calcium, and iron. Such effects as well as osmotic disturbances in the gastrointestinal tract may impose limits on the dietary level of sorbitol that can be tested meaningfully in experimental animals or ingested safely by human beings. These limits are poorly defined at present.

Abnormal glucose metabolism in patients with diabetes mellitus may lead to elevated intracellular concentrations of sorbitol that are associated with cataract formation and neuropathy. However, a role for endogenous sorbitol in these degeneration processes is not established nor are there data indicating that exogenous sorbitol contributes directly to increased concentrations of intracellular sorbitol in lens and nerve cells.

After oral or parenteral administration, sorbitol appears to be metabolized almost exclusively in the liver. Sorbitol is converted enzymatically to glucose and other intermediates of carbohydrate metabolism which can be utilized under normal hormonal control by nonhepatic tissues. Insulin is not required for sorbitol to enter and be converted enzymatically to glucose in hepatic cells.
In human beings, blood glucose levels and insulin response are lower after single oral doses of sorbitol than after equivalent doses of glucose or sucrose. However, data derived from limited short-term feeding of sorbitol with other carbohydrates in a meal suggest no differences in these parameters. If confirmed by longer term feeding trials, these data would indicate that there are no advantages to the well-regulated patient with adult-onset diabetes mellitus offered by partial replacement of glucose or sucrose with sorbitol in meals.

The results of most studies in experimental animals are consistent with the conclusion that sorbitol is less cariogenic than glucose, sucrose, or fructose. There is a need for additional carefully controlled studies on caries development as influenced by the consumption of sorbitol-containing foods.

Animal feeding studies and in vitro tests suggest that sorbitol is not mutagenic, teratogenic, or carcinogenic. However, inconsistent, unconfirmed, and unexplained findings of serum calcium elevation and tissue calcification, altered weights of thyroid and parathyroid glands, adrenal medullary hyperplasia, and possible pituitary chromophobe cell hyperplasia have been reported in experimental animals consuming high dietary levels of sorbitol.
VI. LITERATURE CITED


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