EVALUATION OF THE HEALTH ASPECTS OF MANNITOL
AS A FOOD INGREDIENT

DECEMBER 1972

Prepared for

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

Contract No. FDA 72-85
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
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NOTICE

This report is one of a series of evaluations of the health aspects of the Generally Recognized as Safe (GRAS) food substances that are being made by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology under contract with the Food and Drug Administration of the U. S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office, established in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to make a continuing review, analysis, and evaluation of the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their competence and judgment with due consideration for balance and breadth in the appropriate professional disciplines. Members of the Select Committee on GRAS Substances who have contributed to this report are named in Section VII. The Select Committee's evaluations are being made independently of FDA or any other governmental or nongovernmental group.

These reports are approved by the Select Committee prior to submission to FDA. Although most LSRQ consultants are members of FASEB constituent societies, the reports do not necessarily reflect the views of the Federation as a corporate body or carry the endorsement of the members of its constituent societies.

C. Jelleff Carr
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Life Sciences Research Office
FASEB
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I. INTRODUCTION

Under the terms of FDA Contract 72-85, dated March 30, 1972, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using mannitol as a food ingredient, primarily on the basis of information contained in a monograph summarizing the world's scientific literature from 1920 through 1970, and in certain supplemental documents available as of December 1972. The LSR0 Select Committee on GRAS Substances has reviewed these materials and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of mannitol under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Mannitol occurs in small amounts in a variety of foods such as olives, beets, and celery, and in the exudate of certain trees. It is a solid hexahydric alcohol prepared commercially by catalytic reduction of glucose (1,2).

The Food Chemicals Codex (3) specifies that the food grade product should contain not less than 96 percent mannitol and establishes maximum limits for reducing sugars, heavy metals, and other impurities.

In the food industry, mannitol is used as a conditioning, blending, texturizing, and dispersing agent. It has been used in a wide variety of "sugarless" special dietary food products (2).

Mannitol is present in amounts ranging from 8.0 to 0.004 percent in the following foods, arranged in decreasing order of mannitol content: frostings, nut products, hard candy, and breakfast cereals. It is reported to be present in maximum amounts of 20.0 percent and 32.5 percent in chewing gum and soft candy, respectively (4).

The Food and Drug Administration's GRAS list indicates a tolerance of 5 percent for mannitol in special dietary foods (8). In another order (9) FDA states that mannitol may be safely used in food provided the amount used does not exceed that reasonably required to accomplish the physical or technical effect.

The total poundage of mannitol used in foods in 1970 is reported to be about 90 times that used in 1960 (4). However, the Select Committee has no information to indicate the extent to which the mannitol content of the foregoing food categories has changed in recent years.
III. CONSUMER EXPOSURE DATA

A comprehensive survey by a National Research Council subcommittee (4) has supplied information on the possible daily human intake of mannitol in the total diet, as shown in the following table, for individuals of various age groups. The Select Committee has converted these figures to possible intakes per kilogram of body weight.

<table>
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<tr>
<th>Age group</th>
<th>Possible daily intake</th>
<th>Per kilogram of body weight*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average: mg</td>
<td>Maximum: mg</td>
</tr>
<tr>
<td>0-5 months</td>
<td>65</td>
<td>660</td>
</tr>
<tr>
<td>6-11 months</td>
<td>832</td>
<td>2572</td>
</tr>
<tr>
<td>12-23 months</td>
<td>1240</td>
<td>3353</td>
</tr>
<tr>
<td>2-65+ years</td>
<td>2079</td>
<td>6252</td>
</tr>
</tbody>
</table>

*Calculations based on an average weight of 60 kg for an adult (5) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; 12-23 mos., 11 kg (6).

It is recognized that the figures calculated for the daily intake of mannitol per kg of body weight in the age group 2-65+ years could be deceptively low, since the majority of individuals from age 2 to maturity will probably weigh less than 60 kg. Thus the daily intake of mannitol for children could be significantly higher than the figures indicated. For example, a child weighing 20 kg could consume, on the average, 104 mg per kg rather than 35 mg, and at a maximum, 313 mg per kg per day rather than 104 mg.

However, such deviations from the figures in the table must also be considered in respect to total production and use of mannitol. The data developed by the NRC subcommittee are based on (a) a survey of the frequency of eating various food products, (b) a determination of the portion size of these food products, and (c) a survey of food producers to determine the percentage use of mannitol in these food products (4). The NRC subcommittee has pointed out that its calculations of intakes in most cases are overstated, often by considerable margins. That human

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (4). The Select Committee finds this explanation reasonable, and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey on the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."

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intakes are undoubtedly overstated in the case of mannitol is borne out by the following calculation: The NRC subcommittee has also provided data (4) to show that the use of mannitol for food purposes in the United States was 1,735,065 pounds (789,000 kg) in 1970. This figure is reported to comprise between 60 and 70 percent of the total actual poundage used in food. On the basis of 60 percent adjusted to 100 percent (2.89 million pounds or 1.31 million kg) and a U.S. population of 200 million, the per capita per day average intake would be 18 mg.

On the basis of these considerations, therefore, the Select Committee regards the figures in the table as levels that are not likely to be achieved by any of the age groups.

IV. BIOLOGICAL STUDIES

Mannitol is absorbed from the gastrointestinal tract of animals and man, and does not accumulate in the organism; it is partially metabolized and partly excreted in the urine (10,11,15). There is evidence that the intestinal flora may convert mannitol to more readily utilized substances and this transformation may influence the reported amount of mannitol absorbed and metabolized by the liver (11,13). A wide variety of microorganisms and fungi convert mannitol to sugars and other carbohydrate fragments (14).

The absorption of mannitol in a 50 cm segment of the proximal small intestine, in children varying in age from 8 months to 4 years, has been reported (15). The mannitol was perfused in an isotonic solution in concentrations varying from 50 to 150 millimoles per liter. From 9 to 18 percent of the mannitol was found to be absorbed.

A more extensive study in 16 human adult volunteers, ranging in age from 20 to 66, revealed that, in the oral dosage range of 40 to 100 g, 65 percent of the ingested mannitol was absorbed. Of the absorbed mannitol, about a third was excreted intact in the urine and the remainder was oxidized to carbon dioxide. Excretion was virtually complete by four days, with about 91 percent excreted within the first day (11).

In experiments where 25 g of mannitol were fed to normal men, little evidence was found that the substance was utilized, as measured by blood sugar levels or respiratory quotients. The threshold laxative dose was found to be between 10 and 20 g of mannitol as compared with 50 g of sorbitol (10).

There are no reported long-term animal feeding studies (extending for more than half of the life span of the species) on mannitol. Relevant short-term animal studies and studies on man are summarized below.
The oral LD₅₀ for the mouse is reported to be 22 g per kg, and for the rat to be 17.3 g per kg (18). The minimum lethal dose for the rat is reported to be greater than 13 g per kg (7).

In rats and monkeys fed mannitol (5 percent of the rat diet, and 3 g daily to monkeys) no significant chronic toxicity was observed over a period of 3 months (10). A study on one man, fed 10 g daily for a month, revealed no evidence of toxicity; but the same authors have shown that the ingestion of 10 to 20 g of crystalline mannitol as a part of the diet results in a laxative effect (10). The latter observation has been confirmed (11).

Preliminary teratologic tests in mice, rats, and hamsters have been negative. Oral doses up to 1.6 g per kg of body weight of mannitol to pregnant mice and rats for 10 consecutive days, or up to 1.2 g per kg of body weight to pregnant hamsters for 5 consecutive days, produced no clearly discernible effects on nidation or on maternal or fetal survival. The frequency of abnormalities in either soft or skeletal tissues of the test animals was comparable to that occurring spontaneously in the sham-treated controls (12).

The Select Committee is unaware of any reports on mannitol indicating evidence of its carcinogenicity, mutagenicity, or effects on reproduction.

When injected intravenously, mannitol is filtered by the glomeruli of the kidneys and not appreciably reabsorbed by the tubules (16). For this reason, mannitol has been employed extensively as a substance to measure glomerular filtration rate in man. It has also been used medically as an intravenous diuretic, to lower intracranial pressure, and to decrease intraocular pressure in glaucoma (17). This wide usage of mannitol has not resulted in untoward toxic effects. However, a single allergic reaction to mannitol was observed when the substance was administered intravenously for the treatment of glaucoma (17). In the experience of these investigators, over 1500 patients had received similar medication without a serious allergic reaction. It appears from this report that allergic reactions to mannitol are possible, but that it does not constitute a dietary hazard for this reason.

The Joint FAO/WHO Expert Committee on Food Additives classified mannitol, in amounts of 50-150 mg per kg of body weight daily, as "conditionally acceptable" (18). This term means that the substance may be employed within the specified limits with an adequate margin of safety if it has been reviewed by experts for a particular use.

V. OPINION

The available evidence reveals no short-term toxicological consequences in mice, rats, hamsters, or man when mannitol is fed in amounts exceeding those currently consumed in man's daily diet. There is no evidence that consumption of mannitol in the United States since 1950, when it was first used, has had adverse effects.
It is recognized that mannitol exerts a laxative effect at levels that are from 5 to 10 times the estimated average adult intake level and about 2 to 3 times the maximum adult intake level. Children in the age groups 6-11 months and 12-23 months are now estimated to be consuming mannitol in amounts close to or in excess of those capable of exerting a laxative effect. Recognizing this and also that the reported average and maximum intake levels are generous overestimates, it is the opinion of the Select Committee that the use of mannitol in food in the present or reasonably foreseeable amounts poses no problem in this regard.

The lack of experimental data on long-term studies, carcinogenicity, mutagenicity, or effects on reproduction merits special attention. This is pertinent because of the rapidly increasing use of mannitol in food products.

The Select Committee has weighed the foregoing and concludes that:

There is no evidence in the available literature to show that mannitol constitutes a hazard to the public when used at levels that are now current, or that might reasonably be expected in future.
VI. REFERENCES CITED


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Report submitted by:

January 22, 1973

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