DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR PART 101

[Docket No. 95P–0003]

Food Labeling: Health Claims; Sugar Alcohols and Dental Caries

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to authorize the use, on food labels and in food labeling, of health claims on the association between sugar alcohols and the nonpromotion of dental caries. In addition, FDA is proposing to exempt sugar alcohol-containing foods from certain provisions of the health claims general requirements regulation. FDA is proposing these actions in response to a petition filed by the National Association of Chewing Gum Manufacturers, Inc., and an ad hoc working group of sugar alcohol manufacturers (hereinafter referred to as the petitioners).

DATES: Written comments by October 3, 1995. The agency is proposing that any final rule that may issue based upon this proposal become effective 30 days following its publication.

ADDRESSES: Written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Joyce J. Saltsman, Center for Food Safety and Applied Nutrition (HFS–165), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–205–5916.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Nutrition Labeling and Education Act of 1990

On November 8, 1990, the President signed into law the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) (Pub. L. 101–535). This new law amended the Federal Food, Drug, and Cosmetic Act (the act) in a number of important ways. One of the most notable aspects of the 1990 amendments was that they confirmed FDA's authority to regulate health claims on food labels and in food labeling. As amended by the 1990 amendments, section 403(r)(1)(B) of the act (21 U.S.C. 343(r)(1)(B)) provides that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards contained in regulations adopted by FDA.

Under section 403(r)(3)(B)(i) of the act, the Secretary of Health and Human Services (and, by delegation, FDA) shall promulgate regulations authorizing such claims only if he or she determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

Section 403(r)(3)(B)(ii) and (r)(3)(B)(iii) of the act describes the information that must be included in any claim authorized under the act. The act provides that the claim shall be an accurate representation of the significance of the substance in affecting the disease or health-related condition, and that it shall enable the public to comprehend the information and understand its significance in the context of the total daily diet. Finally, section 403(r)(4)(A)(i) of the act provides that any person may petition FDA to issue a regulation authorizing a health claim.

The 1990 amendments, in addition to amending the act, directed FDA to consider 10 substance-disease relationships as possible subjects of health claims.

B. FDA's Response

In the **Federal Register** of January 6, 1993 (58 FR 2478), FDA adopted a final rule that implemented the health claim provisions of the act. In that final rule, FDA adopted § 101.14 (21 CFR 101.14). The regulation sets out the circumstances in which a substance is eligible to be the subject of a health claim (§ 101.14(b)), adopts the standard in section 403(r)(3)(B)(i) of the act as the standard that the agency will apply in deciding whether to authorize a claim about a substance-disease relationship (§ 101.14(c)), sets forth general rules on how authorized claims are to be made in food labeling (§ 101.14(d)), and establishes limitations on the circumstances in which claims can be made (§ 101.14(e)). The agency also adopted § 101.70 (21 CFR 101.70), which establishes a process for petitioning the agency to authorize health claims about a substance-disease relationship (§ 101.70(a)) and sets out the types of information that any such petition must include (§ 101.70(d)). These regulations became effective on May 8, 1993.

In addition, FDA conducted an extensive review of the evidence on the 10 substance-disease relationships listed in the 1990 amendments. FDA has authorized claims that relate to 8 of these 10 relationships.

The present rulemaking on sugar alcohols and dental caries represents the first rulemaking that FDA has conducted in response to a health claim petition.

C. History of Sugar Alcohol Labeling

In a set of findings of fact and a tentative order on label statements for special dietary foods that the agency issued on July 19, 1977 (42 FR 37166), FDA addressed the issue of the use of the terms ''sugar free,'' ''sugarless,'' and ''no sugar.'' The agency stated that consumers may associate the absence of sugar in a product with weight control and with foods that are low calorie or that have been altered to reduce calories significantly. At that time, FDA viewed foods intended to be useful in maintaining or reducing calorie intake or body weight as foods for special dietary use, that is, as foods intended for supplying particular dietary needs that exist by reason of a physical, physiological, pathological, or other condition.

Evidence had been introduced at a public hearing in the 1977 rulemaking to show that the ''sugarless'' claim is useful to identify foods like chewing gum, which is in sustained contact with the teeth, in which the use of a sweetener other than a fermentable or cariogenic carbohydrate may not promote tooth decay. The secretary of the American Dental Association's Council on Dental Therapeutics supported the importance of advertising and labeling sugarless chewing gum and mints as noncariogenic, in the sense that they did not contribute to the development of dental caries (Ref. 80).

In the final rule on label statements for special dietary foods published in the **Federal Register** of September 22, 1978 (43 FR 43248), FDA required a statement that a food is not low calorie or calorie reduced (unless it is in fact, a low or reduced calorie food) when a ''sugar free,'' ''sugarless,'' or ''no sugar'' claim is made for the food. The agency decided to allow ''useful only in not promoting tooth decay'' as an alternative statement to accompany such claims. The agency stated that the statements that the food is not low calorie or not useful for weight control, as well as ''useful only in not promoting tooth decay,'' were needed because the

term ''sugar free'' meant only that the food was sucrose free. A ''sugar free'' food could contain other fermentable carbohydrates. Thus, the information about the effect of sugar alcohol-containing foods on the risk of developing dental caries was originally placed on the food label primarily to clarify that the product was not necessarily useful in weight control, not to highlight the effect of sugar alcohol on dental caries production.

In the **Federal Register** of November 27, 1991 (56 FR 60421), in response to the 1990 amendments, FDA published a proposed rule entitled ''Food Labeling: Nutrient Content Claims, General Principles, Petitions, Definition of Terms'' (the nutrition labeling general principles proposal). In that document, FDA recognized that developments in nutrition science had established that the focus of nutrient content claims for providing dietary guidance had shifted from special populations with particular conditions to the general population (see 56 FR 60421). Therefore, in the nutrition labeling general principles proposal, FDA proposed to treat several claims that had been subject to regulation in § 105.66 (21 CFR 105.66) as special dietary use claims as nutrient content claims for the general population. To eliminate redundancy in the regulations and to conform § 105.66 to the 1990 amendments, FDA proposed to define these claims in part 101 (21 CFR part 101) and to remove them from part 105 (21 CFR part 105). Specifically, FDA proposed to adopt definitions for terms such as ''low calorie'' and ''reduced calorie,'' for other comparative calorie claims, and for sugar claims under section 403(r)(2) of the act and to codify them in § 101.60. It also proposed to delete these claims from § 105.66.

In the **Federal Register** of January 6, 1993 (58 FR 2302), FDA published its final rules on nutrient content claims. FDA adopted definitions for claims for the calorie content of foods in § 101.60 (58 FR 2302 at 2415). FDA defined claims regarding the sugars content of a food, e.g., ''sugar free,'' ''free of sugar,'' ''no sugar,'' in § 101.60(c). In addition, FDA published a final rule that deleted these claims from § 105.66 (58 FR 2427).

However, based on its consideration of comments on the use of the statement ''useful only in not promoting tooth decay'' to qualify the ''sugarless'' claim, FDA concluded that the statement was actually an unauthorized health claim (58 FR 2302 at 2326). The claim is a health claim because it characterizes the relationship of a substance (sugar alcohols) to a disease (dental caries).

In the nutrient content claim general principles proposal (56 FR 60421 at 60437), the agency stated that it intended to reevaluate the usefulness of chewing gums sweetened with sugar alcohols in not promoting tooth decay. The agency stated that the data supporting the claim were over 20 years old and requested that new data be submitted in accordance with the final rule on health messages. In the nutrient content claim final rule, FDA stated that it had received data on the validity of a claim about this nutrient-disease relationship, and that it would make a determination on whether to authorize a claim in accordance with the final rule on health claims (58 FR 2302 at 2326).

On February 5, 1993, under the procedure established in section 701(e) of the act (21 U.S.C. 371(e)), a group of sugar alcohol manufacturers submitted an objection to the revocation of § 105.66(f) (Ref. 2) and asked for a hearing on their objection. At the same time, the group petitioned for reconsideration of the agency's decision and for a stay of any administrative action by FDA pursuant to the determination announced in the preamble of the nutrient content claims rules that ''useful only in not promoting tooth decay'' is an unauthorized health claim.

Filing objections to the revocation of § 105.66(f) stayed the effect of the final rule as a matter of law. FDA's response to these objections and to the petitions is set forth elsewhere in this issue of the **Federal Register**.

In the **Federal Register** of August 18, 1993 (58 FR 44036), FDA published technical amendments to the health claim regulations in response to comments that the agency received on the implementation final rule that was published with the other final rules that responded to the 1990 amendments in January of 1993 (see 58 FR 2066, August 18, 1993). One of the comments stated that if a petition were submitted for the claim ''Useful Only in Not Promoting Tooth Decay,'' virtually none of the sugar-free products on the market would be eligible to bear the claim based on the requirements of a subsection of health claims general principles regulation, § 101.14(e)(6). FDA acknowledged that certain food products of limited nutritional value that have been specially formulated relative to a specific disease condition, such as dental caries, may be determined to be appropriate foods to bear a health claim (58 FR at 44036). The agency commented that it was its intention to deal with such situations within the regulations authorizing specific health claims. Therefore, FDA amended § 101.14(e)(6) to state that:

> Except for dietary supplements or where provided for in other regulations in part 101, subpart E, the food contains 10 percent or more of the Reference Daily Intake or the Daily Reference Value for vitamin A, vitamin C, iron, calcium, protein, or fiber per reference amount customarily consumed prior to any nutrient addition.

II. Petition for the Noncariogenicity of Sugarless Food Products Sweetened With Sugar Alcohol

A. Background

On August 31, 1994, the petitioners submitted a health claim petition to FDA requesting that the agency authorize a health claim on the relationship of sugar alcohols (i.e., xylitol, sorbitol, mannitol, maltitol, lactitol, isomalt, hydrogenated starch hydrolysates, and hydrogenated glucose syrups) in sugarless foods to dental caries (Ref. 1). On September 15, 1994, FDA sent the petitioners a letter stating that study reports that are needed to support the petition, and that are required for a health claim petition under § 101.70, were not included in the petitioners' submission. The agency stated that no further action would be taken until that information was received (Ref. 3).

On September 27, 1994, the petitioners filed an amendment to their petition submitting the required information. On October 7, 1994, the agency sent the petitioners a letter acknowledging receipt of the additional information and stating that the agency had begun its scientific review of the petition (Ref. 4).

In this document, the agency will consider whether a health claim on the relationship between sugar alcohols and dental caries is justified under the standard in section 403(r)(3)(B)(i) of the act and § 101.14(c) of FDA's regulations. In addition, the agency will consider the petitioners' request that the agency provide in any regulation authorizing a claim that foods sweetened with sugar alcohols be exempt from the requirement in § 101.14(e)(6). The following is a review of the health claim petition.

B. Preliminary Requirements

1. The Substances That Are the Subjects of the Petition

Sugar alcohols are a class of organic compounds that contain chains of carbon atoms that bear two or more hydroxyl groups and have only hydroxyl functional groups (Ref. 1). The hydroxyl groups replace ketone or aldehyde groups that are found in sugars (§ 101.9(c)(6)(iii)). The specific sugar alcohols that are the subject of this petition are xylitol, sorbitol, mannitol,

maltitol, maltitol syrup, maltitol solution, isomalt, lactitol, and mixtures of sugar alcohol substances, i.e., hydrogenated glucose syrup (HGS) and hydrogenated starch hydrolysate (HSH) products.

Xylitol is a monosaccharide polyhydric alcohol with a 5-carbon backbone. It occurs naturally in fruits (e.g., plums, strawberries, and raspberries) and vegetables (e.g., cauliflower and endive) (Refs. 82 and 83). Xylitol is made commercially by the hydrogenation of D-xylose.

Sorbitol is a monosaccharide polyhydric alcohol with a 6-carbon backbone. It is found naturally in many types of berries and fruits and in seaweeds and algae (Ref. 82). Sorbitol is made by hydrogenation of glucose.

Mannitol is also a 6-carbon, monosaccharide polyhydric alcohol. It occurs widely in nature in plants (e.g., pumpkins, mushrooms, onions, beets, celery, and olives), algae, and fungi. Like sorbitol, mannitol is made commercially by the hydrogenation of glucose.

Maltitol is a disaccharide alcohol (4–D-glucopyranosyl-D-sorbitol) with a 12-carbon backbone. It is produced commercially by hydrogenation of maltose.

Lactitol is also a disaccharide alcohol (β-D-galactopyranosyl D-sorbitol) with a 12-carbon backbone. It is produced by hydrogenation of lactose (Ref. 84).

HSH and HGS are mixtures of sugar alcohols manufactured by hydrogenation of corn starch or glucose syrups. The composition of the sugar alcohols in the final product will depend on the manufacturing process. Therefore, HSH and HGS products from different manufacturers may contain different proportions of the same sugar alcohols. One HSH product, under the trade name ''Lycasin,'' was first produced in Sweden by hydrogenation of potato starch. The Swedish product contained a mixture of sorbitol, maltitol, maltotrititol, and hydrogenated dextrines of various molecular weights. When the manufacturing process was moved to France in the 1970's, the production process was also changed (Ref. 85). The French product, ''Lycasin 80/55,'' was made from the hydrogenation of corn starch and contained 6 to 8 percent sorbitol, 50 to 55 percent hydrogenated disaccharides, 20 to 25 percent trisaccharides, and 10 to 20 percent hydrogenated polysaccharides (Ref. 75). Lycasin 80/55, or HSH 80/55, is less fermentable and produces less acid than the Swedish product (Ref. 85).

Isomalt, also known by the commercial name ''Palatinit,'' is an equimolar mixture of the disaccharide alcohols of ∝-D-glucopyranosyl-D-sorbitol and ∝-D-glucopyranosyl-D-mannitol. It is produced by treating sucrose with enzymes, followed by hydrogenation of the resulting mixture.

2. The Substances are Associated With a Disease for Which the U.S. Population is at Risk

Dental caries is recognized in *The Surgeon General's Report on Nutrition and Health* (Surgeon General's report) as a disease or health-related condition for which the United States population is at risk (Ref. 7). The overall prevalence of dental caries imposes a substantial burden on Americans. Of the 13 leading health problems in the United States, dental diseases rank second in direct costs (Ref. 7).

Based on this fact, FDA tentatively concludes that sugar alcohols meet the requirement in § 101.14(b)(1).

3. The Substances Are Food

Sugar alcohols are used as replacements for simple and complex sugars as sweeteners and bulking agents in foods (Ref. 1). Thus sugar alcohols are consumed for their taste and for their effect as a stabilizer and thickener (21 CFR 170.3(o)(28)). Therefore, FDA tentatively concludes that these substances satisfy the preliminary requirements of § 101.14(b)(3)(i).

4. The Substances Are Safe and Lawful

Several of the sugar alcohols that are the subject of this proceeding are currently listed in FDA's food additive and generally recognized as safe (GRAS) regulations, i.e., xylitol (21 CFR 172.395), mannitol (§ 180.25 (21 CFR 180.25)), and sorbitol (§ 184.1835 (21 CFR 184.1835)). Moreover, GRAS affirmation petitions have been submitted for each of the remaining substances, i.e., maltitol (GRASP 6G0319), maltitol syrups (HGS syrups) (GRASP 3G0286), isomalt (GRASP 6G0321), lactitol (GRASP 2G0391), HSH (GRASP 5G0304) and HSH syrups (GRASP 1G0375).

The agency notes that these GRAS affirmation petitions are under consideration and that any positive action resulting from this proposed rule should not be interpreted as an indication that the agency has affirmed those uses of the sugar alcohols as GRAS. Such determinations can only be made after the agency has completed its review of the GRAS petitions. A preliminary review of the GRAS affirmation petitions reveals that they contain significant evidence supporting the safety of these substances.

The agency also points out, however, that some concerns about the safety of sugar alcohols do exist. For example, in a filing notice for the affirmation of the GRAS status of lactitol (58 FR 47746, September 10, 1993), FDA stated that ''the agency's notice of filing of GRASP 2G0391 should not be interpreted either as a determination, preliminary or otherwise, that the issue of Leydig cell tumors has been resolved or that lactitol qualifies for GRAS affirmation.'' Also, by notice in the **Federal Register** of December 13, 1994 (59 FR 64207), the agency announced the filing of a food additive petition (FAP 4A4412) to amend the interim food additive status of mannitol to permit an alternate method of manufacture. In this notice, the agency pointed out concerns about data from studies on mannitol that demonstrate a significant incidence of benign thymomas, and an abnormal growth of thymus gland tissue, in female rats fed mannitol. In addition, the safety of sugar alcohols has been examined by the Federation of American Societies for Experimental Biology (FASEB) (Ref. 90), as well as internationally by the Joint Expert Committee on Food Additives (Ref. 91). The agency also notes that two of the sugar alcohols that are listed in FDA's food additive and GRAS regulations, i.e., mannitol (§ 180.25) and sorbitol (§ 184.1835), require a warning label regarding laxation if daily consumption of these sugar alcohols is expected to exceed 20 grams (g) per day for mannitol and 50 g per day for sorbitol. Nothing in this proposal alters these requirements.

Based on the totality of the evidence, the agency is not challenging, at this time, the petitioner's position that the use of sugar alcohols is safe and lawful. Although FDA tentatively concludes that the petitioner has satisfied the requirements of § 101.14(b)(3)(ii), the agency requests comments on its tentative conclusion.

III. Review of Scientific Evidence

A. Introduction

The development of dental caries is the result of an interaction between sugars (and other fermentable carbohydrates, such as refined flour) and oral bacteria in a suitable environment (Ref. 71). Microorganisms, and *Streptococcus mutans* (*S. mutans*) in particular, in dental plaque metabolize available dietary sugars, producing acid and sticky polysaccharides that adhere to the tooth as plaque. Acid produced from rapid and complete fermentation of sugars creates an acid environment within the

plaque, characterized by a pH of usually less than 5.0, that is capable of demineralizing tooth enamel and causing a carious lesion.

Studies designed to measure the cariogenicity of a food assess the potential to cause caries if it is consumed in a standard way by a highly susceptible subject (Ref. 8). The methods used to measure cariogenic potential include long-term controlled human caries trials, in vivo and in vitro plaque pH measurement, demineralization and remineralization techniques, and rat caries models (Refs. 8 through 11). Because long-term clinical caries trials are difficult to conduct, an integration of the plaque pH, animal caries, and demineralization methodologies has been recommended as the best measure for establishing the cariogenic potential of a food (Ref. 12). Experts recommend, however, that these methods be used with appropriate controls, such as sucrose, to assess experimental results (Ref. 13).

Plaque acidity studies are useful in providing evidence on the effects of many microbial and physiological factors on the cariogenic potential of foods (Ref. 78). An acidic plaque environment at the tooth surface, specifically a pH of less than 5.5, suggests microbial fermentation of a substrate resulting in microbial growth, plaque and acid production, and promotion of carious lesions from enamel decalcification. Factors that can modify these effects include the presence of promoters or inhibitors in food products that affect bacteria growth, the nature of the acids produced as a result of bacterial metabolism of food carbohydrates (Ref. 78), intraplaque buffering, and the pH of mixed saliva (Ref. 74).

B. Review of Scientific Evidence

1. Evidence Considered in Reaching the Decision

The petitioners submitted scientific evidence on the various sugar alcohols and their effects on plaque, plaque pH, and dental caries. This evidence included human (in vivo and epidemiological), animal, and in vitro studies regarding the association between consumption of sugar alcohols from chewing gum and other foods and plaque pH, acid production, plaque quantity and quality, bacteria levels, and the incidence of caries. The petition included four tables that summarized the information for: (1) Human plaque and demineralization, (2) bacteriological studies, (3) animal experiments, and (4) human longitudinal and field studies. A fifth table provided a summary of review articles.

In addition to the information submitted by the petitioner, the agency considered other studies and reviews, such as the reports on health aspects of sugar alcohols by the Life Sciences Research Office (LSRO) and the FASEB (Refs. 14 through 16). The agency also considered the results of additional human epidemiological studies on caries incidence and demineralization; studies of animal caries; and in vitro plaque pH studies.

2. Criteria for Selection of Human Studies

The criteria that the agency used to select pertinent studies were that the studies: (1) Present data and adequate descriptions of study design and methods; (2) be available in English; (3) provide daily intakes of the sugar alcohol or enough information to estimate their daily intakes; (4) include in vivo or in vitro assessment of the changes in plaque pH or plaque acid production; (5) for intervention studies on caries development, be of no less than 2 years (yr) in duration; and (6) be conducted in persons who generally represent the healthy United States' population (adults or children).

In selecting human studies for review, the agency decided that only those studies investigating the use of sugar alcohols in chewing gums and other foods, including mouth rinses that would be representative of beverages, were appropriate for review. The agency excluded studies that were published in abstract form because they lacked sufficient detail on study design and methodologies, and because they lacked necessary primary data. In selecting animal and in vitro studies for review, the agency chose those studies that measured caries development, plaque pH, or acid production from plaque bacteria.

3. Criteria for Evaluating the Relationship Between Sugar Alcohols and Human Dental Caries

The subject of the petitioned health claim is the nonpromotion of dental caries by sugar alcohol-containing foods, especially chewing gum and confectioneries. To support this claim, there needs to be significant scientific evidence to show that the sugar alcohol or sugar alcohol mixture, e.g., HSH, makes no contribution to the progression of dental carious lesions in humans. It would be difficult, if not impossible, to design and execute a study that would directly address this issue because such a study would require a control group that consumed foods containing no sugars, fermentable carbohydrates, or sugar alcohols.

In the absence of studies that directly evaluate the nonpromotion of dental caries by sugar alcohol-containing foods, the agency gave the greatest weight to those studies that evaluated in vivo the acidogenic potential of plaque and plaque pH of sugar alcohols and sucrose in representative food systems (e.g., confectioneries and solutions). These in vivo measures can provide specific information about the effect of sugar alcohols in the oral environment and, more specifically, about the effect of sugar alcohols on pH at the interface between dental plaque and tooth surfaces. The more acidic the environment on the tooth surface, the greater the chance for enamel demineralization and caries formation.

The agency also considered in vitro studies that measured plaque pH and acid production of sugar alcohols in solution, and long-term caries trials that evaluated caries development in a population using foods containing sugar alcohols and sucrose. Studies investigating in situ the demineralization or remineralization of enamel as a result of the action of sugar alcohols on human dental plaque were considered as supporting evidence by the agency.

C. Human Studies

1. Evaluation of Human Studies

FDA evaluated the results of studies against general criteria for good experimental design, execution, and analysis. The criteria that the agency used in evaluating these studies included appropriateness of subject selection criteria; adequacy of the description of the subject's oral health before intervention; extent of evaluation of subject's type of dental plaque (i.e., sticky or nonsticky, thick or thin); methods of plaque collection; adequacy of methods used to assess study endpoints (e.g., in vivo versus in vitro assessment of plaque pH); and other study design characteristics, including randomization of subjects, appropriateness of controls, report of attrition rates (including reasons for attrition), frequency of snack or substance consumption, recognition and control of confounding factors (for example, the subject's use of fluoride during the test period), and appropriateness of statistical tests and comparisons. The agency also considered it desirable if information on treatment and control diets, the sugar alcohol content of the test substance, and daily sugar alcohol and nutrient intakes was available.

A review of the studies evaluating the effect of sugar alcohols on plaque pH and acid production and of the in vitro microbiological studies is provided in Table 1. Table 2 provides a review of epidemiological studies evaluating the incidence of dental caries and studies on demineralization and remineralization.

2. Summary of Evidence Relating Sugar Alcohol and Plaque pH or Acid Production

Bibby and Fu (Ref. 38) measured human plaque pH in vitro using 0.1-, 1.0-, or 10-percent solutions of the following sweeteners: Sucrose, HSH, mannitol, isomalt, xylitol, isomaltulose, sorbose, saccharin, and aspartame. Results showed the lowest plaque pH was attained with sucrose (1- and 10-percent solution: pH less than 5.0). Plaque pH decreased with increasing concentrations of isomalt, sorbitol, mannitol, and HSH. The lowest pH attained for isomalt was about 5.6, for sorbitol 5.82, for mannitol 5.22, and for HSH about 5.0. Negligible acid production was measured from aspartame, saccharin, and xylitol. Solution mixtures of xylitol (5 to 20 percent) and sucrose (10 percent) were fermented to the same low pH as sucrose alone. Thus, the presence of xylitol in a sucrose and xylitol mixture did not affect acid production in plaque from sucrose.

The results of this study support the contention that xylitol does not promote dental caries by lowering plaque pH below 5.5. However, the results for sorbitol, mannitol, isomalt, and HSH do not support a ''nonpromotion'' claim. The results suggest that when higher concentrations of these sweeteners are present in food, the plaque pH may reach a level that will promote decalcification of dental enamel.

Birkhed and Edwardsson (Ref. 39) measured plaque pH and acid production of human plaque samples in solutions of mannitol, xylitol, maltitol, sorbitol, French HSH, Swedish HSH, fructose, and glucose syrups. Results showed that plaque pH in the presence of xylitol, maltitol, mannitol, and French HSH increased or slightly decreased from baseline (pH remaining at 6.8 or above). Sorbitol showed a slight decrease in plaque pH, but the final pH attained was about 6.0. The other sweeteners, including Swedish HSH, depressed plaque pH below pH 6 over the 30-min (min) test period. The results of this study showed that mannitol and xylitol produced no plaque acid compared to sucrose. Maltitol and sorbitol produced plaque acid at rates that were 10 to 30 percent of that of sucrose. French HSH produced 20 to 40 percent and Swedish HSH 50 to 70 percent of the acid produced by sucrose.

Birkhed et al. (Ref. 40) measured acid production in vitro and plaque pH changes in vivo over a 30-min period following a 30-second(s) mouth rinse with 10-percent glucose or sorbitol solutions. To determine whether plaque microorganisms can adapt to the presence of sorbitol, i.e., use it as a source of energy like sucrose, with repeated exposure to the sugar alcohol, investigators measured plaque pH and acid production at the end of a 6-week (wk) period. During the 6-wk period, each subject rinsed their mouth six times per day for approximately 2 min at a time with a 10-percent sorbitol solution. At the end of 6 wk, plaque pH was again measured for a 30-min period following a mouth rinse with glucose and sorbitol. The study results showed acid production in the presence of sorbitol, before adaptation, to be 11.3 percent of that from glucose. After the adaptation period, plaque acid production from sorbitol increased to 30 percent of the glucose rate. After the adaptation period to sorbitol, the glucose rinse produced mean plaque pH values that were higher than before the adaptation period. The differences in plaque pH, however, were only significant at 2 and 5 min following the rinse.

Overall results of this study suggest that sorbitol produces very little plaque acid. Mean plaque pH values after sorbitol adaptation in the presence of the 10-percent sorbitol rinse showed only a slight decrease from the baseline value. The differences in mean plaque pH, compared to baseline, at 5, 10, 20, and 30 min following the rinse were significant. The authors noted that the fermentability of sorbitol was more pronounced after the adaptation period than before.

Birkhed et al. (Ref. 41) studied the effects on in vivo plaque pH and in vitro acid production from HSH (Swedish HSH), maltitol, sorbitol, and xylitol. Subjects in each group sucked on two lozenges a day, containing 0.5 g of one of the four sweeteners and 0.5 g of gum arabic, four times daily between meals (total of eight lozenges per day) for 3 months (mo). Changes in plaque pH over a 30-min period were measured in each of the sugar alcohol groups after a 30-s mouth rinse with a 50-percent solution containing the same sweetener as the lozenge. The rinse was used 1 wk before and 1 wk after the lozenge period. A control group consumed no lozenges but rinsed with each of the four sweeteners. At least 1 wk separated each mouth rinse experiment. Acid production activity (APA) from dental plaque suspended in glucose and each of the four sugar alcohols was determined 1 wk before and 1 wk after the 3-mo consumption period.

The results with HSH showed that although plaque pH values differed before and after the lozenge period, differences were not statistically significant, and that the lowest plaque pH attained was above 6.0. In the maltitol group, plaque pH before the lozenge period was higher than the pH following the lozenge period. Differences at 2, 10, and 30 min were statistically significant. However, there were no significant differences in plaque pH at any time compared to baseline. The lowest plaque pH recorded was about 6.9. Plaque pH in the xylitol group changed very slightly, remaining around pH 7. Plaque pH in the sorbitol group was higher before than after the lozenge period. Differences in pH at times 0 to 20 min and 0 to 30 min before compared with after the test period were statistically significant ($p<0.05$). Final plaque pH values after the 30-min test period were between 6.7 and 7.0. There were no significant differences in plaque pH between the test and control groups using any of the test rinses.

Comparing the APA results for each sweetener with those for glucose showed that HSH was 56 percent of that of glucose 1 wk before the lozenge period and 59 percent of that of glucose 1 wk after the lozenge period. The APA for maltitol compared to glucose was 26 percent (before) and 32 percent (after), sorbitol was 15 percent (before) and 18 percent (after), and xylitol was 0 percent at both time periods. Differences before and after each 3-mo lozenge period were not statistically significant for any of the sugar alcohols.

The results of this study suggest that even though there is some acid production from HSH, maltitol, and sorbitol, the effect on plaque pH in vivo is not detrimental to tooth enamel.

Frostell (Ref. 42) evaluated the effect on plaque pH of sugar solutions and different types of candy and foods. Although the focus of this study was not sugar alcohols, the investigators used sorbitol and HSH as a comparison to sucrose in some of the experiments. Plaque was collected prior to the test period, and its pH was determined. Subjects then rinsed with a test solution or ate a piece of candy or other food being tested. Plaque was collected after 2, 5, 10, 20, and 30 min and its pH was again measured. Sweeteners tested included a sucrose rinse (concentrations from 0.05 to 50 percent), sorbitol tablets (2 g sorbitol), sugar tablets (containing

glucose and sucrose), HSH candy, sugar candies (with sucrose, dextrose, and maltose), marmalades (60-percent HSH or sucrose), and sugar-sweetened sponge cakes, ginger cakes, marshmallows, and chocolates. Results with the sucrose rinses showed that plaque pH decreased with increasing concentrations of sucrose.

Comparing the effects on plaque pH between the sorbitol and sucrose candies results showed that in the sorbitol group's plaque pH increased from about 6.5 (baseline) to 6.9 before returning to baseline. Plaque pH decreased in the sucrose group from 6.5 (baseline) to about 6.0. After 10 min, the pH in the sucrose group slowly increased to about 6.3. Differences in plaque pH between the sorbitol candy and sucrose candy groups were significant at all time periods. In the HSH candy group, plaque pH was significantly higher than that in the group consuming sucrose candy. Differences were significant at all time periods. The lowest plaque pH in the HSH group was above pH 6.3. The group consuming marmalade with HSH experienced a drop in plaque pH to about 6.0 (from 7.0) after 5 min, followed by a gradual increase to a final pH of about 6.5. The group consuming sucrose marmalade experienced a plaque pH of about 5.3 after 5 min, followed by a gradual increase in pH to about 6.0.

Toors and Herczog (Ref. 43) evaluated in vivo plaque pH and in vitro fermentability of an experimental (nonsucrose) licorice in a pooled plaque-saliva mixture. Fermentability (i.e., acid production) of the test substrates was expressed as a percentage of the sucrose licorice. Plaque was collected from 12 volunteers on the day after they consumed 10 pieces of the candy. In vivo plaque pH was measured during and after consumption of licorice by means of pH telemetry. Substrates used in the above tests included sucrose licorice, the experimental licorice, components of the experimental licorice (including sorbitol, potato starch derivative, soy flour, and others), xylitol, hydrogenated potato starch (HPS) (a type of HSH), and a white bread suspension. Results showed the fermentability of the test substrates to be as follows: Potato starch derivative (82 percent), soy flour (75 percent), sorbitol (12 percent), experimental licorice (68 percent), xylitol (5 percent), HPS (60 percent), and white bread suspension (79 percent). In vivo plaque pH results showed sucrose licorice with a minimum plaque pH of about 5.0, experimental licorice with a minimum plaque pH of about 5.5, and a sucrose rinse with a plaque pH of about 4.5.

The results of this study show that food ingredients like soy flour can contribute to the cariogenicity of a food regardless of the presence of a sugar alcohol.

Gallagher and Fussell (Ref. 44) compared the in vitro fermentability of xylitol and other sugar alcohols with sucrose in dental plaque. Plaque collected from adults and children of different ages was incubated in broth culture. Acid production was measured as pH. The control media contained no added carbohydrates.

The results of acid production measurements showed that sucrose was significantly more acidogenic compared to the control and xylitol. Differences were significant. There was no significant difference in acid production between the control groups and the xylitol groups.

Gehring and Hufnagel (Ref. 45) described intra- and extraoral pH measurements of dental plaque. Six adult men and women rinsed for 2 min using one of seven test substances followed by intraoral plaque pH measurements after 3, 4, 5, 7, 9, 13, 17, 21, 27, and 32 min. For the extraoral test, visible plaque was removed, suspended in distilled water, and the pH measured at 3, 5, 7, 9, 11, 15, and 25 min after subjects rinsed with test substances. Test substances included 20 percent solutions of glucose, sucrose, fructose, HSH, mannitol, isomalt, sorbitol, sorbose, or xylitol.

The results of the intraoral plaque pH measurements showed only slight pH decreases within 5 min after administration of xylitol and mannitol, with a return to baseline measures at the end of the 32-min test period. Sorbitol, HSH, isomalt, and sorbose reached a minimum pH just below 6.0 after 5 min followed by a slight increase to about pH 6.1 to 6.4 at the end of the test period. Sucrose, glucose, and fructose showed a minimum pH value of about 4.6 to 4.7 (after 5 min) with an increase to about pH 5.3 to 5.5 at the end of 32 min. Minimum plaque pH by extraoral measurements were higher than the pH according to intraoral measurements. Sucrose, glucose, and fructose minimum pH values ranged from about 5.0 to 5.7 after 5 min and increased to about 5.6 to 6.0 after 32 min. Other pH values were not given. The authors attribute the differences in intra- and extraoral plaque pH measurements to methods in handling plaque removal and the influence of saliva substances.

Havenaar et al. (Ref. 46) evaluated in vitro acid formation from oral bacteria in the presence of sugar substitutes and the influence of xylitol on glucose in growing cultures of *S. mutans*. Fresh isolates of *Streptococci* and other strains were obtained from caries free and caries active subjects. Acid production in 1-percent solutions of glucose (control), sorbose, sorbitol, xylitol, lactitol, maltitol, and HSH was determined by incubating the sweetener in phenol red broth containing oral bacteria. A color change indicated acid formation. Changes in pH was measured after subculturing *S. mutans* in each of the sweeteners, after frequent subculturing in each sweetener to obtain adapted strains of *S. mutans*, and after subculturing the adapted strains once in glucose and resubculturing in the sweetener. Growth of *S. mutans* and pH measurements were also measured in a glucose broth with and without added xylitol.

The results showed no acid production from xylitol or sorbose and acid production from sorbitol, lactitol, and HSH. The authors stated that *S. mutans* slowly fermented maltitol. Results also showed no change in pH with xylitol and a moderate drop in pH to about 6 to 6.5 (actual values not given) with maltitol, sorbitol, lactitol, and HSH after 120 min. Adaptation by *S. mutans* to the sweeteners resulted in a marked increase in fermentation, with final pH values dropping to about 4.5 to 5.5. After one subculturing of the adapted strain in glucose, *S. mutans* lost most of its ability to ferment the sweeteners. The addition of small amounts of xylitol to glucose broth somewhat inhibited acid production from *S. mutans*, but it had no effect on final pH attained.

Jensen (Ref. 47) measured interproximal plaque pH in subjects using five different HSH's and sorbitol and sucrose as controls. Four subjects rinsed with a 5 milliliter (mL) portion of the test solution for 60 min. Plaque pH was then monitored for 30 min. Following the pH measurements, the subject rinsed their mouth with distilled water and chewed paraffin for about 5 min to bring oral pH back to resting levels. The test was repeated with each subject using each of the four test solutions.

The results showed that plaque pH for all test substances remained above pH 6.0 over the 30-min test period. Plaque pH using the sorbitol rinse was similar to that using the test substances. Using the sucrose rinse resulted in plaque pH measurements of approximately 4.0 to 4.1. The identity of the test substances was not provided in this unpublished study. Results indicate that the HSH solutions used in this study were

significantly less acidogenic than sucrose and no different than sorbitol.

Maki et al. (Ref. 48) compared acid production in vivo from isomaltulose, sorbitol, xylitol, and sucrose (control) in human dental plaque. Dental plaque was collected from 12 individuals and incubated with phosphate buffer. After endogenous acid production was measured, a 1-percent solution of the test substance in the same buffer was added, and acid production measured again.

The results showed no acid production in the presence of xylitol. Compared to sucrose (100-percent acid production), acid production from sorbitol was 1 percent. The authors noted that the percent acid production from sorbitol may vary considerably among individuals and with the amount of exposure to sorbitol.

Park et al. (Ref. 49) measured interproximal plaque pH in five subjects after consuming one of three snacks alone or one of three snacks followed by a single mint containing sorbitol (94 percent) or a sorbitol and xylitol blend (79 percent and 15 percent, respectively). When mints were used, they were consumed 3 min following ingestion of the sweet snack. Snacks tested included a sandwich cookie, cupcake, and granola bar. A randomized block design was used to administer the test products and mints (see Table 2 for further details). The lowest plaque pH attained after consuming the three test products without mints ranged from 4.02 to 4.16. When the sorbitol mint was consumed following the test product, mean plaque pH values increased and ranged from 4.68 to 5.04. When the sorbitol and xylitol mint was consumed following consumption of the test products, mean plaque pH increased to a range of 5.32 to 5.60. Differences in mean plaque pH values between the mint products differed significantly when the mints were used after the granola bar and cupcake challenges. There was no significant difference in mean plaque pH between the sorbitol (5.04) and the sorbitol and xylitol mint (5.60) products when these products were used after the sandwich cookie challenge.

The results show that consumption of a sugarless mint reduced the acidogenicity of the test snacks, although final pH values remained below pH 5.5 in all but one test. The authors attributed the results of this study to the stimulatory effects on salivary flow by sugar alcohols. Increasing salivary flow increases the buffering capacity of saliva, thus reducing the acidogenic potential of a variety of snack foods. The authors also attributed the additional buffering effects of the sorbitol and xylitol mint to the presence of xylitol and its potential benefits in reducing plaque microbial activity. Without a sucrose-containing mint as a comparison, however, the influence of sugar alcohols on saliva production cannot be adequately assessed.

Söderling and coworkers (Ref. 50) investigated the effect on dental plaque of chewing gums that contained either xylitol, sorbitol, or a mixture of xylitol and sorbitol and compared the results with those obtained with subjects who used sucrose gums. Twenty-one subjects (adults, ages 19 to 35 yr) who were not habitual gum chewers were randomly assigned to chew gum containing either xylitol, sorbitol, or a blend of the two sugar alcohols for 2 wk. Subjects chewed 10 pieces of gum per day for an intake of either 10.9 g xylitol, 10.9 g sorbitol, or 10.9 g xylitol and sorbitol (8.5 g xylitol and 2.4 g sorbitol). The control group was made up of seven habitual sucrose gum users. Subjects maintained their usual diets and oral hygiene except just before to clinic visits. Interdental plaque pH was collected, and the resting plaque pH determined. Plaque pH was measured at 2, 5, 10, 15, and 20 min after an oral rinse containing the same sugar alcohols as used in the gum. Afterward, subjects rinsed with water and chewed a piece of paraffin for 1 min to expedite removal of sugar alcohols from the mouth. Baseline pH was again measured, followed by a mouth rinse with 10 mL of 10-percent sucrose. Plaque pH was again determined.

The results from using gum for 2 wk showed no significant changes in resting plaque pH in the xylitol and xylitol and sorbitol groups, whereas the use of sorbitol gum was associated with a lower pH. Final plaque pH values after use of sorbitol gum were significantly lower than baseline values, but all final values remained above pH 6.0.

Birkhed and Skude (Ref. 51) evaluated, among other tests, the APA from glucose, soluble starch, and Swedish HSH in dental plaque. Eleven adults were instructed to avoid oral hygienic procedures for 2 days. No dietary changes were required. At the end of 2 days, plaque was collected. The APA was determined from 3-percent solutions of glucose, boiled soluble starch, and HSH. The APA was also determined in increasing concentrations (0.003 to 12 percent weight per volume (w/v)) of starch and HSH.

The results showed significantly lower ($p<0.001$) APA from soluble starch (75.7 percent) and HSH (61.5 percent) compared to glucose (99.7 percent). The APA from HSH was also significantly lower ($p<0.01$) than that from soluble starch. The range of optimum acid production for both substrates was 0.03 to 6 percent. The authors noted that Swedish HSH is more fermentable than French HSH, which contains less high molecular weight hydrogenated saccharides than Swedish HSH.

Grenby et al. (Ref. 76) evaluated the dental properties of lactitol compared to five other bulk sweeteners, i.e., sucrose, glucose, sorbitol, mannitol, and xylitol, in vitro using a standardized mixed culture of dental plaque microorganisms. Sweeteners were incubated for 24 hours (h) in media containing a 1-percent solution of one of the six sweeteners. Plaque microorganisms were also incubated in media containing the sweeteners with segments of intact surfaces or with segments of pulverized dental enamel. The demineralization action of the acid produced by microbial fermentation was assayed by calcium and phosphorous analyses.

The greatest amount of acid production and lowest pH (significantly different than the sugar alcohols) were reported with sucrose and glucose (pH of 4.0 to 4.3). Lactitol and xylitol showed only slight changes in pH and acid production over the 24 h (final pH of 6.1 to 6.3); whereas sorbitol and mannitol showed slight changes in pH during the first 12 h ($pH \geq 6$), then gradually decreased to a final pH of 4.6 to 5.1 after 24 h.

The results of the demineralization test showed highly significant differences ($p<0.001$) between sucrose and glucose and the sugar alcohols. The reductions in calcium and phosphorous dissolving in sorbitol was approximately 80 to 85 percent, mannitol 63 to 69 percent, and lactitol and xylitol 94 to 98 percent compared to mineral loss in the presence of glucose.

3. Summary of Evidence Relating Sugar Alcohol and Dental Caries: Long-Term Studies

Möller and Poulsen (Ref. 20) determined the effect of long-term chewing of sorbitol chewing gum on the incidence of dental caries, plaque, and gingivitis. The sorbitol chewing gum contained calcium phosphate which acts as a buffer in saliva to help maintain pH and aid remineralization. Two groups of children, ages 8 to 12 yr of age, from two different schools in Denmark took part in this 2-yr study. Group 1 chewed one piece of sorbitol-containing gum three times a day, after meals. Group 2 chewed no gum and

served as the control. At the start of the study, subjects in group 1 had more decayed and filled toothsurfaces than the control group; however, the differences were not statistically significant.

The results showed that the sorbitol group had a significantly lower incidence of dental caries compared to the control after 2 yr. The control group, which did not chew gum, did not experience the same salivary stimulation from the chewing of gum, nor did they have an equivalent source of calcium phosphate. These are large confounders in this study. The authors noted a number of factors that could contribute to the observed results, such as the sorbitol content of the chewing gum, reduced consumption of sugar-containing sweets, intra-examiner variability, and other unknown conditions.

Bánózcy et al. (Ref. 21) evaluated the effect of sorbitol-containing sweets on the caries increment of children aged 3 to 12 yr, in a clinical longitudinal study planned for 3 yr. The test group consumed 8 g of sorbitol per day between meals, while the control group consumed a similar amount of sucrose-containing sweets.

The results showed that mean decayed, missing, or filled (DMF) values for teeth in the sorbitol group were 1.09, 0.90, and 1.18 in the first, second, and third yr, respectively. The sucrose group had mean DMF values of 2.61, 1.86, and 1.13 for the first, second, and third yr, respectively. The differences in caries increments were significant ($p<0.001$) in the first and second yr but not in the third yr. The authors noted that the lack of significance in the third yr may be attributed somewhat to a lack of subject compliance since the children in the sorbitol group traded sweets with the sucrose group, in addition to other factors. Results of this study indicate that sorbitol is less cariogenic than sucrose.

Kandelman and Gagnon (Ref. 22) reported on the incidence and progression of dental caries in school children after 12 mo of a 2-yr study using xylitol in chewing gum. The subjects were 433 children, ages 8 to 9 yr old, from 13 elementary schools, and were from low socioeconomic areas with a high caries rate. The children were assigned to one of three groups: A control group that received no chewing gum and chewed no gum while at school, a test group that received gum containing 15-percent xylitol and 50-percent sorbitol (XYL15), and a second test group that received gum containing 65-percent xylitol (XYL65). Students were not randomly assigned to groups. Rather, an entire class was assigned to one of the three groups. The XYL65 group consumed 3.4 g xylitol per day, and the XYL15 group consumed 0.8 g per day.

The results showed significantly lower net progression of decay (NPD) (i.e., the difference in the number of reversals from the progressions of decay for each child) in the XYL65 group (1.25) than in XYL15 group (1.87) ($p< 0.05$), and each xylitol group had significantly ($p<0.001$) lower NPD than the control. The decayed, missing, filled surfaces (DMFS) increment was also significantly lower in the xylitol groups compared to the control. There was no significant difference in DMFS between the gum groups. Results of this study suggest that chewing gum containing xylitol or a blend of xylitol and sorbitol provided more benefits for teeth than not chewing gum at all.

Rekola (Ref. 23) compared the progression of incipient carious lesions on buccal smooth surfaces in subjects participating in the 2-yr Turku sugar study (Ref. 24). Subjects consumed either a diet containing sucrose or one with almost complete replacement of sucrose products with xylitol-containing products. The progression of carious lesions were assessed by use of color dental photographs of the right and left sides and of the front of maxillary and mandibular teeth.

The results showed that the sucrose group had a significant tendency for increased size of carious lesions over the 2-yr period compared to the group consuming xylitol ($p<0.01$). The white spot lesions in the xylitol group were significantly smaller than those in the sucrose group.

Rekola (Ref. 25) quantified changes in the size of approximal carious lesions in subjects after 2 yr of almost complete substitution of dietary sucrose with xylitol (Ref. 23). Bitewing radiographs were taken during the 2-yr study. In this study, the radiographs were projected onto a planimetry plate so that the area of the lesions could be determined. The sizes of the lesions at the different time periods were compared, and the rate of caries progression was also compared. At the beginning of the study, there was no difference in the mean size of carious lesions between groups. The size of the approximal lesions, i.e., lesions that were neither filler nor overlapping at 0 and 24 mo, in the sucrose group increased significantly ($p<0.001$) over 2 yr compared to the lesions in the xylitol group. The lesion size in the xylitol group remained virtually unchanged.

The authors reported a trend towards decreasing lesion size in canines and first molars compared to molars and second premolars in the xylitol group. This trend was not observed in the sucrose group. Results of these studies support the observation that xylitol is less cariogenic than sucrose.

In a World Health Organization (WHO) field trial in Hungary (Ref. 26), the effects of a partial substitution of sucrose for xylitol in the diets of 689 institutionalized children, ages 6 to 11 yr, were examined. The xylitol group used fluoride dentifrice and consumed no more than 20 g of xylitol per day in chewing gum, chocolate, hard candy, and wafers. The fluoride group received fluoride in dentifrice, water, and milk, but consumed no xylitol products. The control group received no fluoride treatment and consumed no xylitol-containing products. After 3 yr, the xylitol group had a statistically significant ($p<0.001$) lower incidence of caries compared to the control and fluoride groups. The authors noted that results from this study were obtained under conditions where caries prevalence and incidence were still high. Results of this study support the observation that xylitol-containing products are less cariogenic than sucrose-containing products.

In a 2-yr substudy (Ref. 28) of the WHO xylitol field studies in Hungary (Ref. 26), Scheinin and coworkers assessed the caries increment with systemic fluoride (fluoride group) and restorative treatment only (control group). This study differed from the 3-yr study primarily in baseline differences. Children entering the institutions during the first yr of the 3-yr study were included in this substudy.

The substudy showed similar favorable results with xylitol compared to the control. The caries increment was 3.8 in the xylitol group, 4.8 in the fluoride group, and 6.0 in the control group. The differences in caries increment between the xylitol group and the other two groups were significant ($p<0.001$). Results again supported a lower incidence of caries when xylitol is substituted for sucrose in the diet.

In a WHO field trial in Thailand and French Polynesia (Ref. 29), the usefulness of a fluoride rinse, fluoridated sucrose chewing gum, and fluoridated xylitol (51 percent) and sorbitol gum in controlling dental caries was evaluated in children over a 3-yr period. In French Polynesia, a fourth group used nonfluoridated chewing gum sweetened with xylitol (51 percent) and sorbitol. Approximately 250 children at each of the ages 6 to 7 yr, 9 to 10 yr, and 12 to 13 yr were examined. The 12- to 13-yr age group was intended to provide data for

comparison with the 9- to 10-yr old group, who would be ages 12 to 13 yr at the end of the study.

The results from the Thailand study showed that the fluoridated xylitol and sorbitol gum group had lower decayed, missing, and filled teeth (DMFT) and DMFS scores than either the fluoride rinse group or the fluoridated sucrose gum group. Results from the French Polynesia study showed that the subjects started with much higher DMFT and DMFS mean scores initially than the subjects in Thailand. Although the results with the fluoride gum sweetened with the sugar alcohols were better than any of the other treatments, the overall caries incidence in this population is very high. The presence of fluoride in the chewing gums confounds the results of the sugar alcohols. The authors describe this study population as a community experiencing an increase in the prevalence of the disease. This study group does not reflect the general population of the United States.

In another WHO field trial, Kandelman and coworkers (Ref. 30) evaluated the effects of xylitol intervention on dental caries in French Polynesian children, ages 7 to 12 yr. Of 746 subjects enrolled in this 32-mo study, 468 completed the study. Subjects in the xylitol groups consumed 20 g of xylitol daily in various food products, such as chewing gum, hard candy, chocolate, and gumdrops. The control group received no xylitol-containing products.

The results showed significantly reduced caries increment rate by 37 percent to 39 percent in the xylitol groups compared to the controls. This study was neither randomized nor blinded. Results support the observation that xylitol-containing products are less cariogenic than the sucrose-containing products.

Frostell and coworkers (Ref. 31) determined the effect on caries increment in children, ages from 2½ to 4 yr, of substituting HSH for sucrose in candy. During this 1½- to 2½-yr study, subjects in the test group consumed candies made with HSH and chewing gum made with sorbitol. The control group consumed sucrose candies and gum. Investigators monitored the intake of candies by use of coupons which the parents used at local stores to buy the candy. An analysis of the coupons used showed that parents of the children in the test group used a smaller number of coupons than the parents of the children in the control group. Based on inquiries, the investigators discovered that the parents of the subjects in the HSH group had also given the children other candy in addition to HSH candy. The consumption of HSH candy was reported from 50 to 75 percent of the total candy consumption.

The results showed no significant differences in caries scores after 1½ to 2½ yr with HSH candy consumption compared to sucrose candy consumption. When investigators analyzed the data of those children whose parents consumed the correct candy for their group, the differences in caries increment between the groups were still not significant but showed a trend towards a lower incidence of caries in the HSH group. The results of this study were confounded by poor compliance, inter-examiner variability, lack of blinding, and inconsistent results and do not support significant dental benefits from the use of HSH.

Glass (Ref. 32) evaluated the cariogenicity of sorbitol chewing gum with regular use by children, ages 7 to 11 yr old, living in a nonfluoride area. In this 2-yr study subjects were randomly assigned to either a no-chewing group (control) or to the one which chewed gum twice daily. Subjects in the gum group were provided two sticks of gum daily for use at school and four sticks of gum for use at home when school was not in session.

The results showed that over the 2-yr study period, mean caries increments were 4.6 new decayed and filled (DF) surfaces for the sorbitol gum group (n=269) and 4.7 new DF surfaces for the no-gum group (n=271). The difference between the groups was not statistically significant. Although the results of this study suggest that adding sorbitol-containing gum to the diet did not result in any additional dental caries, the effect of chewing gum per se on the incidence of dental caries was not considered.

4. Summary of Evidence Relating Sugar Alcohol and Dental Caries: Short-Term Studies

Ikeda et al. (Ref. 33) evaluated the cariogenicity of maltitol and a polysaccharide alcohol using an intraoral cariogenicity test (ICT) and rat tests. Most of the details of the methods used in the ICT were not provided, making the results difficult to interpret. Bovine enamel fragments were extraorally dipped in 3-percent solutions of sucrose (control), maltitol, or the polysaccharide alcohol for 1 min every day. After 1 wk, hardness was measured. The higher the value for hardness means a softer enamel and a greater loss of enamel.

The results showed a decalcification score for maltitol of 1.66 compared to a score of 2.70 for sucrose. These differences were significant. In the animal study, one group was provided a feed with 26-percent maltitol and 30-percent starch, a second group was provided a feed with sucrose instead of maltitol, and a third group consumed a diet without sucrose. Results showed a caries score of 45.8 for the sucrose group, 3.2 for the maltitol group, and 5.2 for the no-sucrose group. Differences between the sucrose group and the other groups were statistically significant.

Yagi (Ref. 34) evaluated the effects of maltitol on changes in enamel hardness. Enamel decalcification was measured using an ICT with a denture containing two bovine enamel slabs. Four subjects wore the dentures for 7 days. Each day, one enamel slab was exposed to a 3-percent maltitol solution and the other to a 3-percent sucrose solution. Enamel hardness was measured at the end of the wk.

The results showed that the average change in hardness compared to pretreatment levels for the enamel in maltitol was 1.47 micrometers compared to 3.35 micrometers for the enamel in sucrose. Differences between the two measurements were significant. The authors noted that there were considerable differences in individual responses to sucrose and maltitol. They attributed these differences to the oral environment (e.g., plaque bacteria and quality and quantity of saliva). However, general observations were that sucrose causes significant loss of enamel, as evidenced by changes in enamel hardness, compared to the effect of maltitol on tooth enamel.

Leach et al. (Ref. 35) evaluated in situ the effect on remineralization of artificial caries-like lesions in human enamel with sorbitol. Ten adult subjects wore cast bands containing enamel on one lower first molar tooth for two 3-wk periods during which they continued to use normal oral hygiene procedures. Artificial caries lesions were made in each enamel slab and covered with gauze to encourage the formation and accumulation of plaque on the enamel surface. Subjects were given snack foods (chocolate bar, raisins, cream-filled wafers, and cream-filled, iced cupcake) and instructed to consume one each morning and afternoon between meals. During the first experimental period, subjects chewed, for 20 min each, five sticks per day of commercial sugarless gum after meals and snacks. The gum was sweetened primarily with sorbitol and small amounts of mannitol, HGS, and aspartame. During the second experimental period, snacks were consumed but without chewing gum (control).

The results showed statistically significant ($p<0.001$) remineralization during both experimental periods compared to the original lesion. The difference between the remineralization with and without gum was also significantly different ($p<0.01$), indicating overall promotion of remineralization by gum chewing. The authors attributed the remineralization during the nongum period to the presence of gauze used with the intraoral device to collect plaque. The gauze could have concentrated calcium and phosphates from the diet in plaque and fluoride from dentifrice. It is not known what effects the duration and timing of the gum chewing had on the results. Without a comparison to sucrose-containing gum and a nonsweetened gum, it is not possible to evaluate the effect of chewing gum for 20 min.

Rundegren et al. (Ref. 36) evaluated in situ the effect on demineralization of sucrose substitutes in a 4-wk test. Intraoral devices containing bovine enamel mounted on acrylic blocks were used with group 1. Partial dentures with enamel slabs were used with group 2. Sweeteners tested included 10 percent solutions of sucrose, maltitol, and HSH. Sucrose was used as the positive control, and 0.9-percent solution of sodium chloride was used as a negative control. Subjects immersed the test sites of their appliances in the test sweetener four times a day for a 10-min period. Plaque was collected at the end of 4 wk and plated to determine the content of *S. mutans*. The degree of demineralization was measured by evaluating changes in microhardness of the enamel. The buffering capacity of whole saliva was evaluated weekly by measuring final pH in a mixture of 1 mL of saliva and 3 mL of sodium chloride.

The results showed a higher degree of demineralization overall in the adults (ages 56 to 59 yr) using the partial dentures compared to students (age 19 yr) using an intraoral device. Results from the test ($n=4$) of enamel microhardness in HSH versus sodium chloride suggest that HSH does not contribute to demineralization, and that measured changes in microhardness reflected the background of fermentable carbohydrates in the diet. Comparing the differences in microhardness of enamel slabs between the sucrose and HSH diets and the sucrose and maltitol diets showed that sucrose results in significant demineralization compared to the sugar alcohols.

Creanor et al. (Ref. 37) evaluated the effect of chewing gum for 20 min on in situ enamel lesion remineralization compared to a fluoridated dentifrice. Artificial enamel lesions were created in vitro in sound human enamel and mounted for wearing just opposite the lower first and second molars. Baseline mineral contents were measured. Subjects used a fluoridated dentifrice twice daily and maintained their regular diets. Six subjects chewed five sticks of chewing gum containing sorbitol and some HGS and aspartame after each meal and snack. The gum was chewed for 20 min in order to minimize any deleterious effects of sucrose. Six other subjects received no gum and served as the control. At the end of 7 wk, the test subjects became the control group, and the control subjects became the new test group. The new test group then chewed sucrose-containing gum for 7 wk.

The results showed that after using sugar-free gum for 7 wk, the degree of mineral loss for the enamel corresponded to a remineralization value of 18.2 percent. After 7 wk of chewing sucrose gum, the percent remineralization was calculated to be 18.3 percent. The difference between the sorbitol and sucrose gum groups was not significant. Results of this study suggest that chewing gum for 20 min, regardless of the sweetener, can be beneficial to dental health.

A common problem in studies evaluating the dental health benefits of sugar alcohol-containing chewing gum is the absence of an appropriate control group. Most of the studies that have been done use a control group that does not chew gum. Ideally, to evaluate the relationship of sugar alcohol-sweetened chewing gum in not promoting dental caries, the control group would chew an unsweetened gum product. Such a group is needed to take into consideration the effects of chewing gum itself on the endpoint measure, e.g., plaque pH or plaque acid production. Chewing gum is known to stimulate saliva, which can help neutralize oral acids, raise plaque pH, and help to promote enamel remineralization in some circumstances. It would be considered unethical by standards in the United States to use a control group that chews sucrose-containing gum and, as a consequence, puts the subjects at risk of dental disease, in order to compare the incidence of dental caries to that from a sugar alcohol-containing gum.

The few long-term caries field trials that were submitted with this petition show how multiple problems in the execution of clinical studies can easily confound the results. Problems often include subject compliance, reporting and control of dietary intake, selection of appropriate control foods, inter- and intraexaminer variability, subject attrition, and inability to blind the study. The majority of these trials compared sucrose consumers to individuals who had partial or complete substitution of sugar alcohols for sucrose. The results consistently demonstrated significantly fewer caries in the group consuming sugar alcohols than in the group consuming sucrose.

Although the relationship between some of the sugar alcohols and promotion of dental caries has not been well studied in humans, it is becoming increasingly evident that sugar alcohols, when substituted for sucrose and other fermentable carbohydrates, may provide important dental health benefits for the consumers of those products.

D. Animal Studies

FDA reviewed over 20 animal studies investigating the effects of sugar alcohol consumption on the incidence of dental caries or on the acidogenic potential of dental, *S. mutans*, or mixed oral microorganisms. Most of the animal studies that have been done to test the effect of sugar alcohols on the incidence of caries were programmed feeding studies using weanling rats. The animals were usually divided into groups and fed diets containing different test sweeteners. The control diets were either a basal diet with no carbohydrate sweeteners or sugar substitutes or a basal diet with added sucrose. The test diets were administered over a period of weeks, increasing the sugar substitute concentration slowly to allow the animals time to adapt to the specific sweetener and to minimize the severity of diarrhea, a side effect of sugar alcohol consumption that increases with increasing concentration of the sugar alcohol.

Investigators also evaluated the general health and growth of the animals during the experimental period. Many animals, and rats in particular, do not like the taste of sugar alcohols and, therefore, will eat less of the test diet and increase their intake of water. Most investigators monitored the animals' total dietary intake to ensure that consumption patterns were similar between the control and test animals.

A potential confounding factor in these studies is the effect of total food and water intake on caries development. If animals consume less of a sugar alcohol diet compared to the control animals consuming a sucrose diet, any significant differences in caries incidence may actually be attributable to the differences in food and water consumption and not to an effect of the sugar substitute. Some studies reported a lower survival rate in animals on the

sugar alcohol diets. This finding made interpretation of the results more difficult because of uneven group sizes.

In order to promote the cariogenic process, the animals were inoculated with either mixed strains of plaque bacteria or purified strains of *S. mutans* and other microorganisms found in dental plaque. Experimental periods lasted, on the whole, for 60 to 70 days. These periods included the time given for the animals to adapt to the test diets.

Havenaar et al. (Ref. 52) fed *S. mutans* inoculated rats one of six diets 18 times a day: The basal diet plus 50-percent starch, or the basal diet plus 30-percent starch and 20 percent of either sucrose, HSH's, xylitol, sorbitol, or L-sorbose. In a second experiment, the rats were fed the same diets 14 times a day and alternated with the basal diet containing 20-percent sucrose and 10-percent glucose (four times a day). In both experiments, the starch, HSH, xylitol, and L-sorbose groups showed significantly less fissure lesions than the sorbitol and sucrose groups. The sorbitol group showed significantly less fissure caries in the mandibular molars with respect to the severity of the lesions compared to the sucrose group.

Havenaar et al. (Ref. 53) in five successive experiments, fed rats ad libitum on diets containing sucrose or HSH 80/55. In each experiment, the rats were inoculated with plaque from rats in the previous experiment (Ref. 52). Results showed that compared to sucrose, HSH was relatively noncariogenic. The incidence of fissure caries in the mandibular molars for rats consuming 20-percent sucrose was 13.1, whereas the fissure caries incidence in rats consuming 20-percent HSH was 1.5 to 2.5 ($p<0.001$).

Havenaar et al. (Ref. 54) evaluated the usefulness of diets for testing the caries promoting or inhibiting properties of sugar substitutes. The investigators fed two groups of rats experimental diet 2000 containing 50-percent sucrose and 14-percent starch or 50-percent sucrose, 9-percent starch, and 5-percent xylitol for a period of 42 days. Results showed no significant differences in caries incidence between the sucrose starch, the xylitol group and the sucrose and starch group. In another experiment animals were fed diet SSP 20/5 containing 20-percent sucrose, 5-percent glucose, and 25-percent starch or 20-percent sucrose, 5-percent glucose, 20-percent starch, and 5-percent xylitol for a period of 66 days. Results showed the xylitol, sucrose, and starch group to have significantly fewer caries (12.3 caries versus 14.8) compared to the sucrose, starch, and glucose group.

Havenaar and coworkers (Ref. 55) fed one group of rats a basal diet containing 20-percent sucrose, 5-percent glucose, and 25-percent starch. The test group received the basal diet with 20-percent starch and 5-percent xylitol and fluoride. After 54, 75, or 96 days, rats were crossed over to the other diet for an additional 21 to 42 days. Results showed that the xylitol group had significantly fewer fissure caries than the sucrose group. The authors also reported that the longer the experimental period, the more severe the caries, irrespective of the presence of xylitol. After crossover, total numbers of caries did not change, but the xylitol group showed significantly fewer initial lesions compared with the mean caries incidence in the sucrose group on day 54.

Grenby and Colley (Ref. 56) fed a control group of rats a cariogenic diet containing 46-percent sucrose and fed two test groups the same cariogenic diet either with 20 percent of the sucrose replaced with xylitol, sorbitol, mannitol, or wheat starch (experiment A). The animals consuming sorbitol and mannitol did not remain healthy during the experiment, so this part of the experiment was terminated. The animals consuming xylitol also experienced difficult health effects at first but later improved and were returned to the 20-percent xylitol diet. In experiment B there were only two diets: A cariogenic diet with 46-percent sucrose and an experimental diet with 10 percent of the sucrose in the diet replaced with xylitol.

In experiment A, significantly fewer caries were experienced only in the group consuming the sucrose and xylitol diet compared to the control group. In experiment B, the level of caries was high for both the sucrose group and the sucrose and xylitol group. The overall caries scores were not significantly different.

Karle and Gehring (Ref. 57) evaluated the effect of sugar alcohols and sucrose on both xerostomized (salivary glands removed) and nonxerostomized rats. The control group consumed a basal diet without sweetener. Test groups received the basal diet plus sucrose, xylitol, isomalt, or other sweeteners. Sweetener concentrations were increased over a 3-wk period to a level of 30 percent of the diet. The xerostomized rats had more caries with all substances than the nonxerostomized rats. Sucrose was shown to be the most cariogenic sweetener, and xylitol the least cariogenic, in the nonxerostomized rats. Both the xylitol and isomalt groups had significantly fewer caries than the sucrose group.

Mühlemann and coworkers (Ref. 58) compared the cariogenicity of diet 2000 (containing 64-percent wheat flour) to the same diet containing xylitol or sorbitol (15 percent and 25 percent of the flour replaced) or sucrose (15 percent and 25 percent of the flour replaced). Sweetener mixtures containing 15-percent sucrose and 15-percent xylitol or sorbitol and 25-percent sucrose and 25-percent xylitol or sorbitol were also substituted for the flour ingredient of the basal diet. The rats consuming diets with 15- and 25-percent sucrose experienced 17.3 and 17.8 smooth surface caries, respectively. Rats consuming animal chow with 15-percent xylitol or sorbitol experienced 0.0 and 1.9 smooth surface caries, respectively. The caries score for the control group was 4.9. The highest number of fissure caries (11.3) occurred in the 25-percent sucrose group. The control group had 5.1 lesions. Substituting xylitol (25 percent) in the diet resulted in fewer caries (0.2) compared to the control, but differences were not significant. Twenty-five percent sorbitol in the diet produced a caries score of 2.8.

Shyu and Hsu (Ref. 59) evaluated the cariogenicity of 10-percent xylitol, mannitol, sorbitol, and sucrose in rats fed a plain basal diet. A control group was fed the basal diet without sweetener. Caries evaluations were made on the 45th and 90th days of feeding. The xylitol group had 86 percent fewer caries (significant) compared to the sucrose group and 76 percent fewer caries than the control. The mannitol group experienced 70 and 51 percent fewer caries than the sucrose and control groups, respectively. The sorbitol group experienced 48 and 14 percent fewer caries than the sucrose and control groups, respectively.

Bramstedt et al. (Ref. 60) evaluated the cariogenicity of isomalt, xylitol, and sucrose in 60 rats divided into five groups. The control diet was a basic diet containing half synthetic feed. Another control group received a special basic diet containing no low molecular weight carbohydrates. The test groups received the basic diet with increasing doses of sweetener up to 30 percent of the diet. The sucrose group had a significantly higher number of caries than either of the sugar alcohol groups. The group consuming the special basic diet had the lowest incidence of caries. There were no significant differences in the number of caries between the basic diet, xylitol, and isomalt groups, although the isomalt group showed a slightly higher incidence of caries.

Izumiya et al. (Ref. 61) fed rats 10 or 20 percent by weight of sweeteners in

feed. Rats consuming a dietary feed containing 10-percent maltitol had significantly fewer caries than the sucrose group. Details of this study and the results were not given in this reference.

Gehring and Karle (Ref. 62) evaluated the cariogenic properties of isomalt, in comparison to those of sucrose and xylitol in the basal diet of conventional and gnotobiotic (i.e., specially reared laboratory animals in which the microflora are specifically known) rats. The final concentration of sweetener in the feed was 30 percent. A second experiment was performed using isomalt, xylitol, sorbitol, and sucrose in chocolate. The basal diet constituted 40 percent of the total diet, and the chocolate constituted 60 percent. The isomalt group had significantly fewer caries than the sucrose group, and the xylitol group had significantly fewer caries than the isomalt group. The second experiment showed significant differences in caries experience after the T (initial caries lesions) and B (advanced caries) stages between the sucrose and sorbitol chocolate groups, the sorbitol and isomalt chocolate groups, and also between the isomalt and xylitol chocolate group. The order of cariogenicity of the test substances was sucrose greater than (>) sorbitol > isomalt > xylitol > control. An in vitro microbiological experiment was performed to test acid production capacity of plaque microorganisms in 10 percent solutions of isomalt, glucopyranosido mannitol (GPM), glucopyranosido sorbitol (GPS), sorbitol, mannitol, sucrose, and fructose. GPS and GPM are the two components that make up isomalt. Sucrose produced acid rapidly and had the greatest acid formation. Sorbitol and mannitol produced acid slowly, and isomalt and its two components had practically no acid production in vitro.

Karle and Gehring (Ref. 63) evaluated the cariogenicity of isomalt in rats. Six groups of rats received the basic diet without low molecular weight carbohydrates in addition to xylitol, sorbose, isomalt, lactose, and sucrose. The control group received only the basic diet. Sweetener concentrations were increased slowly up to 30 percent by weight of the basic feed. The highest number of fissure caries were caused by sucrose (about 33) followed by lactose (25), isomalt (about 13), sorbose (about 12), xylitol (about 7) and the control (5). Differences in caries incidence between the sucrose and the other groups were significant.

Larje and Larson (Ref. 64) fed rats a caries diet, diet 2000, to which various sweeteners were added. The caries diet, containing 56 percent sucrose, was used as a control ration. Sucrose substitutes used in at least one of the experiments included glucose, fructose, mannitol, sorbitol, potato starch, starch/sucrose mixtures, or HPS (contains sorbitol and hydrogenated dextrins). In the first experiment each group was fed diet 2000 for a few days, then they were changed to one of the diets containing a sucrose substitute. Each test diet was fed for 7 out of every 14 days followed by rotation back to the control diet. The diets were changed every 2 or 3 days according to a predetermined schedule. A second experiment was designed to determine the effect of feeding the sucrose diet after the period of bacterial implantation on diets containing sucrose substitutes. The animals consumed one of the test diets the first week while being inoculated with *S. mutans*, followed in the final 7 wk by the control diet containing sucrose. A third experiment was designed to determine the effect of feeding sucrose and sucrose-substitute diets intermittently after the period of bacterial implantation on the sucrose diet. The animals consumed diet 2000 the first wk, followed in the final 7 wk by diets containing the sugar substitutes.

The results of the first experiment showed significantly ($p<0.001$) fewer smooth surface caries with all sugar alcohols, potato starch, dextrose, and hydrogenated starch compared to the sucrose group. Significantly ($p<0.05$) fewer sulcal caries were experienced in the groups receiving mannitol, sorbitol plus starch, potato starch, and HPS compared to the sucrose group. The authors observed that in all of the experiments, every group in which sucrose was restricted, whether by dietary substitution or by shortened feeding periods, developed significantly fewer caries on smooth surfaces compared to the sucrose control animals. The animals in the mannitol, sorbitol plus starch, and sorbitol groups consumed less food during the test period compared to the sucrose controls. The authors stated that food consumption and weight gains were directly related to the incidence of caries.

The results of experiment 2 showed significantly ($p<0.001$) fewer smooth surface caries in groups fed hydrogenated starch, potato starch, dextrose, fructose, sorbitol plus starch, dextrose plus fructose compared to the sucrose group. Groups receiving HPS, fructose, and sorbitol plus starch experienced significantly ($p<0.001$) fewer sulcal caries compared to the sucrose group.

The results of experiment 3 showed significantly ($p<0.001$) fewer smooth surface caries in groups receiving potato starch, fructose, sorbitol plus starch, dextrose plus fructose, dextrose, and hydrogenated starch compared to the sucrose group. The overall results showed that reducing the exposure to sucrose results in fewer carious lesions.

Mühlemann (Ref. 65) tested the effects of topical applications of sugar substitutes on caries incidence and bacterial agglomerate formation in rats receiving a cariogenic diet containing 20-percent sucrose. Sweeteners tested (50 percent w/v) included the following: Sucrose, mannitol, GPS, GPM, isomalt, sorbitol, maltitol, and French HSH. Three control groups were used: (1) One group received the cariogenic diet (20-percent sucrose) and no topical applications, (2) the second group received a topical application of water with the cariogenic diet, and (3) the third group was treated topically with chlorhexidin digluconate (0.5 percent) as a positive control. Topical solutions were applied five times a day for 23 days.

Among the carbohydrates treatments, the isomalt, GPS, and GPM groups had the lowest incidence of fissure and smooth surface caries. The differences, however, between the caries incidence in these three groups and the other test groups were not statistically significant. The incidence of caries in the chlorhexidine control group was statistically significantly lower than all treatment groups. The control groups receiving no application and water both experienced slightly more caries than the sugar alcohol groups. Results of these studies suggest that in the presence of a cariogenic diet, topical application of mannitol, isomalt, sorbitol, maltitol, or HSH does not affect the promotion by sucrose of dental caries in rats.

Ooshima et al. (Ref. 66) evaluated the cariogenicity of maltitol in rats infected with *S. mutans*. Animals were divided into 12 groups. Group A received a control diet containing 56-percent wheat flour. Groups B through L received the same diet as the control group but had portions of the wheat flour replaced with one of the test substances. The sweeteners tested were as follows: 10-percent maltitol plus 46-percent wheat flour (group B), 20-percent maltitol plus 36-percent wheat flour (group C), 10-percent sucrose plus 46-percent wheat flour (group D), 10-percent sucrose plus 10-percent maltitol plus 36-percent wheat flour (group E), 20-percent sucrose plus 36-percent wheat flour (group F), 20-percent sucrose plus 20-percent maltitol plus

16-percent wheat flour (group G), 24-percent sucrose plus 32-percent wheat flour (group H), 24-percent sucrose plus 16-percent maltitol plus 16-percent wheat flour (group I), 28-percent sucrose plus 28-percent wheat flour (group J), 28-percent sucrose plus 12-percent maltitol plus 16-percent wheat flour (group K), or 40-percent sucrose plus 12-percent wheat flour (group L).

The results of this study showed that the maltitol did not induce dental caries in groups B and C compared to the wheat flour alone (group A). Groups A, B, and C experienced significantly ($p<0.001$) fewer caries than the sucrose group (group L). Groups D through I and K reported significantly ($p<0.001$ and $p<0.01$, respectively) fewer caries than group L. There was no significant difference in caries score between group J (equal parts sucrose and wheat flour) and group L. Thus, this study suggests that replacing sucrose with less cariogenic sweeteners or wheat flour results in fewer dental caries in rats.

Tate et. al. (Ref. 67) reported on the correlations between progressive caries and sugar intake in hamsters inoculated with S. *mutans.* Animals were fed a diet with 10-percent sucrose (group 1), 20-percent sucrose (group 2), 10-percent sucrose plus 10-percent maltitol (group 3), 10-percent sucrose plus 10-percent coupling sugar (group 4), 10-percent maltitol (group 5), or 10-percent coupling sugar (group 6). Group 2 experienced the most caries. There was no significant difference in caries score between group 1 and groups 3 and 4. Groups 5 and 6 had significantly ($p<0.01$) fewer caries than groups 1 or 2. This reference did not provide sufficient details regarding the methodology and analysis of results for purposes of evaluating the weight of the results.

Leach and Green (Ref. 68) fed two groups of rats a basal diet supplemented with sucrose plus 3-percent xylitol or 6-percent xylitol. The control group consumed the basal diet with sucrose. In experiment 1, rats were continuously fed the same diet during the experimental period. In experiment 2, rats were fed diets alternating between the control diet one day and the test diet the next day. In experiment 1, rats fed the sucrose and 6-percent xylitol mixture had significantly ($p<0.02$) fewer fissure caries than the control. There were no significant differences in the xylitol mixture groups. In experiment 2, both xylitol mixture diet groups had significantly ($p<0.001$) fewer fissure caries than the control. There were no significant differences among the xylitol mixture groups.

Mukasa (Ref. 69) evaluated the cariogenicity of maltitol and SE58 in rats. Product SE58 is a highly purified corn starch treated with enzyme and hydrogenated. It contains 20- to 25-percent sorbitol, 20- to 30-percent maltitol, 15- to 25-percent maltotrititol, and 30- to 40-percent maltopentaitol. In experiment one, three groups of rats were fed diet 2000 containing either 56-percent sucrose, maltitol, or SE58, among other ingredients. Because the rats consuming the maltitol and SE58 diets experienced serious growth problems, experiment one was discontinued. In experiment two, the level of all sweeteners in diet 2000 was reduced to 26 percent, with the remaining 30 percent as added corn starch. The sucrose group had a mean fissure caries score of 31.5 and a smooth surface caries score of 14.1. The maltitol group had 3.1 fissure caries and no smooth surface caries. The SE58 group had 4.6 fissure caries and 0.5 smooth surface caries. Differences between the sucrose group and each sugar alcohol group were significant.

Van der Hoeven (Ref. 70) evaluated the cariogenicity of isomalt in rats. Test diets consisted of a base diet containing 16-percent sucrose and 44-percent wheat flour and a base diet with 16-percent isomalt and 44-percent wheat flour. The control diet consisted of 60-percent wheat flour and no added sweetener. Diets were offered ad libitum over a period of 14 wk. Results showed increasing incidence of dentinal fissure lesions in the sucrose group (wk 2 = 4; wk 14 = 14 lesions) and almost no caries in the isomalt group (wk 2 = 0; wk 8 = 4; wk 14 = 1 lesion). There was no difference in the incidence of caries between the isomalt and the control groups.

Van der Hoeven (Ref. 73) evaluated the cariogenicity of lactitol in program-fed rats. The sweetener was incorporated into a powdered diet, described by Havenaar et al. (Ref. 54), consisting of a basic part (50 percent), wheat flour (25-percent), and test substance (25-percent). Lactitol was compared with sorbitol, xylitol, sucrose, and a control with wheat flour in addition to the basic part. The animals received 9 g of diet divided into 18 portions of 0.5 g each per day. The animals on the xylitol and sorbitol diets were reported to experience reduced weight gains and a reduced appearance of the fur. None of the animals suffered from diarrhea.

There were significantly fewer caries in the xylitol, lactitol, sorbitol, and wheat flour groups compared to the sucrose group. The incidence of caries in the lactitol and sorbitol groups was slightly, but not significantly, higher than in the wheat flour group. The incidence of caries was lowest in the xylitol group.

In a twofold experiment using caries-active rats, Grenby and Phillips (Ref. 77) evaluated: (1) The cariogenicity of lactitol, sucrose, and xylitol at a level of 160 g per (/) kilogram (kg), a level stated to approximate the average sucrose content of the diet in developed countries, and (2) the cariogenicity of lactitol in a sweet biscuit compared to a sucrose-sweetened biscuit. In the first experiment, the sweetener was incorporated into a laboratory chow containing white flour, skim milk powder, liver powder, and a vitamin-mineral supplement. In the second part of the experiment, biscuits, containing 166 g of lactitol/kg, were incorporated into the animal chow for a final concentration of lactitol of 110 g/kg. Animals were fed the diets for a period of 8 wk. Experiment 1 showed highly significant differences in caries score, total number of lesions, and severity of lesions in the sugar alcohol groups compared to the sucrose controls. The sugar alcohol groups had very few caries, and differences between groups were not significant. The animals in both the xylitol and lactitol groups required several weeks to adapt to the diets, showing increased water intake and decreased food intake. Because of poor physical condition, only 11 of the 22 rats in the xylitol group completed the full 8-wk test. Animals on the sucrose diet were significantly heavier than the sugar alcohol animals.

Results of the second test showed highly significant differences between the lactitol- and sucrose-biscuits groups in all caries parameters. The average caries score for the lactitol group was less than one per animal. Weight gains, however, were consistently lower, and water intake increased in the lactitol group.

The results of the above animal studies show that animals fed sugar alcohols in animal chow had fewer and less extensive caries than animals fed sucrose. The studies also show that, in general, rats do not eat as much of a sugar alcohol-containing diet as a sucrose-containing diet and, therefore, tend to gain less weight and have more physiological problems.

E. Summary of Human and Animal Studies

1. Xylitol

In its 1978 review of the studies on xylitol, FASEB concluded that xylitol appeared to be noncariogenic in studies evaluating the effect of sucrose

replacement with xylitol and in studies evaluating the effect of partial replacement of sucrose with xylitol in chewing gum (Ref. 14). However, FASEB concluded that it was essential that these studies be replicated by other workers in order to confirm the observations and conclusions.

Rekola (Refs. 23 and 25) conducted a followup assessment of results from the 2-yr Turku sugar study evaluating the progression of incipient carious lesions and lesion sizes on buccal smooth surfaces with dietary substitution of xylitol for sucrose. In the 2-yr Turku sugar study, dietary xylitol was almost completely substituted for sucrose. Subjects were assigned to groups based on individual preference. Rekola examined color dental photographs, taken during the 2-yr study, of 33 subjects in the sucrose group and 47 subjects in the xylitol group. The xylitol group showed significantly smaller white spot lesions and had a significantly lower caries score compared to the sucrose group.

Results of several more recent human caries studies (Refs. 22, 26, and 28 through 30) reported significantly fewer caries in the xylitol group compared to the sucrose group. Kandelman and Gagnon (Ref. 22) reported significantly less NPD and incidence of DMFT in school children chewing three sticks per day of xylitol gum (3.4 g) or xylitol and sorbitol gum (0.9 g xylitol and 2.4 g sorbitol) compared to the nongum control group. Results of xylitol field studies in Hungary (Refs. 26 and 28), French Polynesia (Refs. 29 and 30), and Thailand (Ref. 29) conducted by WHO showed lower caries incidence and caries increment rate in children consuming xylitol and sorbitol in chewing gum (Ref. 29) and xylitol in other snack foods (Ref. 30) compared to a nonsugar alcohol group. However, results of the gum study in French Polynesia and Thailand (Ref. 29) were confounded by the presence of fluoride in the gums tested. In addition, the prevalence and incidence of dental caries in these population groups were high and increasing and do not reflect the general healthy population of the United States.

The effect of xylitol on acid production or plaque pH was studied in ten studies (Refs. 38, 39, 41, 43 through 46, 48, 50, and 76). In nine of these (Refs. 38, 39, 41, 43 through 46, 48, and 50), xylitol was found to result in negligible to no acid production with little to no change in plaque pH. Similarly, results showed no significant effect of xylitol on resting plaque pH. Plaque pH from exposure to xylitol was always significantly higher than that of sucrose or glucose.

Twelve animal studies (Refs. 52, 54, 56 through 60, 62, 63, 68, 73, and 77) evaluated the effects of xylitol on dental caries in rats or hamsters. Eight of these (Refs. 52, 57 through 60, 62, 63, and 77) used a test diet that contained only one sweetener, either sucrose or xylitol. In all of these studies, there were significantly fewer caries reported in animals consuming the basal diet with xylitol compared to sucrose controls. The incidence of caries was also significantly less in the xylitol group compared to animals consuming isomalt (Ref. 63) and sorbitol (Ref. 52). The concentrations of xylitol in the test diets ranged from 10 percent up to 30 percent by weight.

Results of the animal studies evaluating the effect of xylitol in diets containing sucrose (Refs. 54, 56, 68, and 73) showed mixed results depending on the concentrations of sucrose and xylitol in the test diets. Havenaar et al. (Ref 54) showed no significant difference in caries in animals consuming a diet with sucrose and 5-percent xylitol, but a significant difference in caries when the sucrose was lowered to 20-percent of the diet and xylitol 5-percent. Grenby and Colley (Ref. 56) reported a high caries level in animals consuming either a diet containing 46-percent sucrose or 36-percent sucrose and 10-percent xylitol. The caries score was significantly lower in rats consuming a diet with 26-percent sucrose and 20-percent xylitol compared to the 46-percent sucrose diet. An in vitro microbiological test showed no acid production by S. *mutans* from xylitol. Van der Hoeven (Ref. 73) reported significantly fewer caries in rats consuming a diet with 25-percent xylitol compared to the rats consuming a basic diet with 25-percent sucrose. The xylitol group also had fewer caries than the wheat flour control group.

2. Sorbitol

In its March 1979, review of sorbitol in health and disease (Ref. 15), FASEB reviewed available animal and human studies regarding the cariogenicity of sorbitol. FASEB concluded that the weight of evidence from animal studies suggests that sorbitol is less cariogenic than sucrose, fructose, glucose, and dextrin. Based on the human studies published in the early to mid-1970's, FASEB noted that the results do not provide definitive data on the effect of sorbitol on the caries process. It noted that the results of studies on plaque pH suggest that sorbitol is slowly fermented to plaque pH levels of about 6. It also said that some studies have provided evidence of adaptation of oral flora after long-term use of sorbitol-containing products. FASEB noted that a human population that regularly consumes sorbitol-containing foods, such as jams and jellies, baked goods, or other food products, has not been identified and studied to establish whether sorbitol significantly alters the carious process.

Two studies submitted with the petition evaluated the cariogenicity of sorbitol in chewing gum (Refs. 20 and 32), and one study (Ref. 35) evaluated the effect of sorbitol in chewing gum on demineralization of enamel. Möller and Poulsen (Ref. 20) reported an increased number of sound tooth surfaces and a smaller caries increment rate in children consuming sorbitol gum containing calcium phosphate compared to the control group that did not consume chewing gum. However, the presence of calcium phosphate, which acts as a buffer in saliva to help reduce its acidity, and the absence of gum chewing in the control group, confound these observations.

Glass (Ref. 32) reported no significant differences in the number of DF surfaces or teeth in children using sorbitol chewing gum for 2 yr compared to a no-gum group. This study, however, did not consider the effect of chewing gum per se on dental caries.

Leach et al. (Ref. 35) conducted an intraoral test in subjects fitted with bands containing human enamel with artificial white spot lesions. The subjects consumed sucrose-containing snacks. During one of the test periods, the subjects chewed gum containing sorbitol with small amounts of mannitol, HGS, and aspartame, for 20 min at a time after each meal and snack. The study showed significantly more remineralization during the sorbitol gum period compared to baseline and the no-gum (sucrose) period. Results of this study are confounded, however, because of the duration (i.e., 20 min) and timing (i.e., immediately after meals and snacks) of the gum chewing. In addition, the effect of sorbitol alone cannot be determined because of the presence of other sugar alcohols and aspartame in the test gum.

Bánóczy et al. (Ref. 21) reported a significantly lower caries increment in children consuming sorbitol-containing sweets between meals compared to children consuming sucrose-containing sweets between meals over a 2-yr period. Differences between groups were not significant during the third yr of this study, however, the authors attributed the lack of significance during the third yr to the trading of sweets between groups.

Twelve studies evaluated changes in plaque pH after exposure to sorbitol-sweetened mouth rinses (Refs. 39 through 41, 45, and 47), solutions (Refs. 38, 46, and 76), tablets (Ref. 42), mints (Ref. 49), chewing gum (Ref. 50), and licorice (Ref. 43). Plaque pH changes in the presence of sorbitol decreased from baseline pH but remained approximately at or above a pH of 6.0 (Refs. 39 through 42, 45 through 47, and 50). Bibby and Fu (Ref. 38) reported progressively decreasing plaque pH values in vitro with increasing concentrations of sorbitol in a concentrated plaque suspension. Only slight decreases in pH were reported in 0.1- to 1.0-percent solutions. In the presence of a 10-percent sorbitol solution, plaque pH dropped to about 5.8. Grenby et al. (Ref. 76) reported a pH of about 6.0 after 12 h and a final pH in vitro of about 4.6 after 24 h of incubating concentrated plaque with 10-percent sorbitol. The results of these studies suggest that higher concentrations of sorbitol may lead to further decreases in plaque pH to a level that may become detrimental to tooth enamel (i.e., at or below pH 5.5).

Park et al. (Ref. 49) found that use of sorbitol mints or mints with a blend of sorbitol and xylitol helped reduce the acidogenic potential of certain snack foods, although final pH values remained low. Toors and Herczog (Ref. 43) showed that plaque pH is affected by more than the sweetener component of a food. Results of plaque pH in vivo with an experimental licorice, containing sorbitol, soy flour, and potato starch derivative among other ingredients, showed a minimum pH of about 5.5. A sucrose-containing licorice used in this study lowered plaque pH to about 5.0. The fermentability of both the potato starch derivative (82 percent) and soy flour (75 percent) contributed to the observed changes in plaque pH in the experimental licorice. The fermentability of sorbitol in the experimental licorice was 12 percent.

Five studies (Refs. 39 through 41, 43, and 48) measured the APA of plaque with sorbitol. In all cases, sorbitol was fermented slowly with a reported range of acid production of 10 to 30 percent compared to sucrose or glucose. The higher acid production rate (i.e., 30 percent) was attributed to adaptation to sorbitol by *S. mutans* and other plaque microorganisms capable of fermenting carbohydrates. Havenaar et al. (Ref. 46) also reported a marked increase in fermentation of sorbitol and other sugar alcohols after multiple subculturing of plaque microorganisms with the sugar alcohol. However, the investigators reported that adaptation to sorbitol and other sugar alcohols was lost after subculturing once in glucose.

Results of animal studies evaluating sorbitol (Refs. 35, 52, 58, 59, 62, 64, and 73) showed significantly fewer caries in the sorbitol group than in the sucrose group. However, use of sorbitol resulted in more caries compared to animals consuming other sugar alcohols, such as xylitol and HSH (Refs. 52, 64, and 73). The concentration of sorbitol in these studies ranged from 10 percent up to 56 percent.

3. Mannitol

In its August 1979, review of mannitol in health and disease, FASEB (Ref. 16) reviewed available animal and human studies regarding the effect of mannitol on acid production, plaque pH changes, and changes in microhardness of bovine enamel in an ICT. It noted that human plaque studies in vivo or in vitro found that plaque pH decreases from 0 up to 1.0 units over a 30-min test period. FASEB concluded that the results were consistent with the results of animal experiments showing that mannitol, in the absence of adaptation of the oral microflora, is less cariogenic than sucrose.

Bibby and Fu (Ref. 38) measured in vitro plaque pH changes, over a 20-min incubation period, in the presence of increasing concentrations of mannitol (0.1-, 1.0-, and 10-percent concentrations) in a concentrated plaque suspension. Results showed that plaque pH decreased with increasing concentrations of mannitol. Final plaque pH values were 5.67, 5.54, and 5.22, respectively. Similar plaque pH values were reported by Grenby et. al. (Ref. 76). Results of the Grenby study showed that a 1-percent solution of mannitol, when incubated for 24 h with concentrated plaque and pieces of a human molar tooth, resulted in slight acid production and pH decrease over a 12-h period, but that after 24 h, the final pH was about 5.1. However, results from an in vitro demineralization test showed very little loss of calcium and phosphorus, significantly less than the loss of minerals with glucose.

Results of other studies, however, show that mannitol results in little change to plaque pH. Birkhed and Edwardsson (Ref. 39) reported only slight changes in plaque pH following use of a mouth rinse with a concentrated solution of mannitol. In addition, they reported an acid production rate from mannitol in dental plaque suspension of 0 percent compared to sucrose (100 percent). Gehring and Hufnagel (Ref. 45) used intraoral measurements to evaluate the effect of sugar alcohols on plaque pH. Results of plaque exposed to a 20-percent mannitol solution showed the minimum pH obtained was slightly above 6.0. The plaque samples in these two studies were not concentrated as they were in the study by Bibby and Fu (Ref. 38) or by Grenby et al. (Ref. 76), which may account for the differences in plaque pH values reported for mannitol solutions. The results of one other in vitro microbiological study, with 10-percent mannitol and an incubation time of 48 h (Ref. 62), support the observation that mannitol is fermented very slowly, resulting in little acid production and small pH changes.

Animals fed mannitol (Refs. 59 and 64) or maltitol (Refs. 66, 67, and 69) showed significantly fewer caries compared to animals fed sucrose diets. The concentrations of the sugar alcohols in these studies ranged from 10 to 56 percent. An in vitro microbiological study (Ref. 62) showed that a 10-percent solution of mannitol was fermented very slowly.

4. Maltitol

Three studies (Refs. 33, 34, and 36) measured the effects on enamel decalcification of maltitol and sucrose solutions using an ICT with bovine enamel fragments adhered to a partial denture. Ikeda and coworkers (Ref. 33) showed significantly more decalcification in the presence of sucrose as compared to maltitol. Additional rat caries tests were in agreement with the results of the ICT. Rats fed a diet with maltitol had significantly fewer caries than the sucrose group. In this study maltitol was almost noncariogenic. Yagi (Ref. 34) reported significantly harder enamel after exposure to maltitol than after exposure to sucrose. Lack of details in this study, however, make it difficult to completely interpret the results. Rundegren (Ref. 36) reported significantly less enamel demineralization with maltitol compared to sucrose. The authors associated the changes that they observed in enamel hardness in the maltitol group with the effects of other dietary carbohydrates and not maltitol. Sucrose was found to exert an effect on enamel hardness that is not related to the effects of other dietary carbohydrates.

Three studies (Refs. 39, 41, and 46) evaluated plaque pH or acid production in maltitol. Birkhed and Edwardsson (Ref. 39) measured in vitro acid production and pH changes in human dental plaque following the use of various sweeteners in a mouth rinse. The results with maltitol showed an acid production rate of 10 to 30 percent

of that of sucrose. Changes in plaque pH in the presence of maltitol showed only a slight decrease from baseline pH (about pH 6.9).

Birkhed et al. (Ref. 41) measured in vivo pH changes in human dental plaque after subjects consumed lozenges sweetened with various sweeteners for 3 mo and then rinsed with a mouth rinse sweetened with the same sweetener as in the lozenge. A sucrose mouth rinse was also used by each sweetener group. Results with maltitol showed small, but some significant, changes in plaque pH compared to baseline pH (about pH 7.0) over the 30-min test period. The lowest plaque pH recorded, however, was about pH 6.8. In vitro acid production with maltitol was found to be about 26 to 32 percent of glucose.

Havenaar et al. (Ref. 46) measured changes in pH and acid production in vitro in growing cultures of oral bacteria obtained from caries active and caries free subjects. Results showed that a 1 percent solution of maltitol was slowly fermented to acid by plaque bacteria. Cell suspensions of *S. mutans* in maltitol showed pH decreased from a baseline of about pH 7.0 to about pH 6.5. Adaptation of *S. mutans* by frequent subculturing in maltitol showed a marked increase in fermentation by *S. mutans*. However, the ability to ferment the sugar alcohol was lost after one subculturing of the adapted strain in glucose.

5. Lactitol

Havenaar et al. (Ref. 46) showed that a 1 percent solution of lactitol was fermented by *S. mutans* and *Actinomyces*. Cell suspensions of *S. mutans* in lactitol showed pH decreased from a baseline of about pH 7.0 to about pH 6.5 or above after a 2-h incubation period. Adaptation of *S. mutans* by frequent subculturing in lactitol showed a marked increase in fermentation by *S. mutans* to give a plaque pH of about 5.0. However, the ability to ferment the sugar alcohol was lost after one subculturing of the adapted strain in glucose. Grenby et al. (Ref. 76) showed that a 1-percent solution of lactitol, when incubated for 24 h with human plaque and pieces of a human molar tooth, resulted in slight acid production and a final pH of about 6.3 and almost no loss of calcium and phosphorus from tooth enamel.

Results of two animal studies (Refs. 73 and 77) showed that substitution of lactitol for sucrose in laboratory chow resulted in significantly fewer caries in the lactitol group compared to the sucrose group. The lactitol group (Ref. 73) experienced slightly, but not significantly, more caries than the xylitol group and the wheat flour control group and fewer caries than the sorbitol group. There was no significant difference between the caries score in animals fed lactitol-containing or xylitol-containing chow (Ref. 77). There were significantly fewer caries in animals fed lactitol-containing biscuits compared to the sucrose biscuit group (Ref. 77). The average caries score in the lactitol biscuit group was less than one per animal.

6. Isomalt

Two studies investigated the effects on plaque pH with isomalt (Refs. 38 and 45). Bibby and Fu (Ref. 38) measured pH changes in fresh plaque from adult volunteers with increasing concentrations of isomalt. Results showed that as the concentration of the sugar alcohol increased, the pH of the plaque decreased. The range of plaque pH values reported for isomalt was from 6.6 (0.1 percent solution) to approximately 5.7 (10-percent solution). Gehring and Hufnagel (Ref. 45) reported a minimum plaque pH of about 6.0 after 5 min with isomalt. This value increased gradually over the next 27 min to about pH 6.3. As discussed above, the methods and type of dental plaque must be considered when comparing the results of these studies.

Results of animal studies with concentrations of isomalt from 16 to 30 percent of the rat diet showed significantly fewer caries compared to sucrose diets (Refs. 57, 60, 62, 63, 65, and 70). The caries incidence was high in xerostomized rats consuming either sucrose or isomalt (Ref. 57). The isomalt group of nonxerostomized rats, however, had significantly fewer caries than the sucrose group.

7. HGS and HSH

Frostell et al. (Ref. 31) studied the effect on caries increment in children of substitution of HSH for sucrose in candy. The results of this study are confounded for a number of reasons (see Table 2) and do not support a significant dental benefit from the use of HSH candies in place of sucrose-containing candies.

Rundegren et al. (Ref. 36) measured enamel hardness in the presence of sucrose, sodium chloride, or HSH using an ICT. The investigators reported significantly less enamel demineralization with HSH. The results of the study were that only sucrose promoted demineralization over and above the effect of dietary carbohydrates. The authors attributed the demineralization measured in the presence of HSH to the effect of dietary carbohydrates.

Eight studies measured plaque pH changes from exposure to HSH in solutions (Refs. 38 and 46), rinses (Refs. 39, 41, 45, and 47), and candy (Refs. 42 and 43). Bibby and Fu (Ref. 38) showed that as the concentration of HSH increased, plaque pH decreased. The lowest plaque pH value (10-percent solution of HSH) obtained was about 5.0. Havenaar et al. (Ref. 46) showed that a 1-percent solution of HSH was fermented by *S. mutans* and Actinomyces. Cell suspensions of *S. mutans* in HSH showed a pH decrease from a baseline of about pH 7.0 to about pH 6.5. Adaptation of *S. mutans* by frequent subculturing in HSH showed a marked increase in fermentation by *S. mutans* to give a plaque pH of slightly below 6.0. However, the ability to ferment the sugar alcohol was lost after one subculturing of the adapted strain in glucose.

Birkhed and Edwardsson (Ref. 39) measured plaque pH in vitro following the use of a mouth rinse containing Swedish or French HSH. French HSH appeared to have little effect on plaque pH. Plaque pH values remained slightly below or at 7.0. Swedish HSH showed a decrease in plaque pH within 5 to 10 min to just less than pH 6.0. Over the remaining 20 min, the pH increased to just over 6.0. Birkhed et al. (Ref. 41) measured pH changes in human dental plaque after subjects consumed lozenges sweetened with Swedish HSH for 3 mo and then rinsed with a mouth rinse sweetened with Swedish HSH. Plaque pH was also measured after a sucrose mouth rinse. The results of the study showed that HSH resulted in a drop in plaque pH in all tests; however, the minimum pH values reached were above 6.0. Gehring and Hufnagel (Ref. 45) reported an intraoral plaque pH change with a HSH rinse (20 percent solution) from about pH 6.6 to about 5.6.

Jensen (Ref. 47) showed interproximal plaque pH values from five different HGS rinses were statistically significantly different compared to the sucrose control. Differences between the HGS test solutions and a sorbitol control were not significantly different. The minimum pH values obtained with the HGS solutions were above pH 6.0. Composition of the HGS test substances was not provided.

Frostell (Ref. 42) reported a slight decrease in vitro plaque pH (from about 6.7 to about 6.5) after subjects consumed HSH candy. After consuming a sucrose lozenge, plaque pH decreased to about 5.8. A sucrose solution resulted in a minimum plaque pH of about 5.3. Toors and Herczog (Ref. 43) showed that plaque pH is affected by more than the sweetener component of a food. Results

of plaque pH in vivo with an experimental licorice, containing soy flour, HPS, and potato starch derivative among other ingredients, showed a minimum pH of about 5.5. The fermentability of the HPS (60 percent), potato starch derivative (82 percent) and soy flour (75 percent) contributed to the observed changes in plaque pH in the experimental licorice.

Acid production in vitro was reported in two studies (Refs. 39 and 51). Birkhed and Edwardsson (Ref. 39) reported an acid production rate from French HSH of 20 to 40 percent and from Swedish HSH of 50 to 70 percent compared to glucose syrups. Birkhed and Skude (Ref. 51) reported significantly lower acid production rates (i.e., slower rate of fermentation) from a 3 percent solution of Swedish HSH (61.5 percent) compared to glucose (99.7 percent). The investigators also reported that HSH was metabolized significantly more slowly than soluble starch.

Results of animal studies evaluating the effect of HSH showed the sweetener to be relatively noncariogenic compared to sucrose (Refs. 52, 53, 64, and 69). Differences in the incidence of caries between the sucrose and HSH groups were significant.

IV. Decision To Propose a Health Claim Relating Sugar Alcohols To the Nonpromotion of Dental Caries

FDA limited its review of the scientific evidence relating sugar alcohols and dental caries to those studies evaluating changes in plaque pH, plaque acid production, decalcification or remineralization of tooth enamel, and the incidence of dental caries with sugar alcohols. FDA considered these limitations to be appropriate because previous Federal government and other authoritative reviews had focused on these areas (Refs. 14 through 16), and the majority of research efforts to date have focused on these areas.

FDA tentatively concludes that, based on the totality of publicly available scientific evidence regarding the relationship among sugar alcohols, plaque pH, and dental caries, there is significant scientific agreement to support the relationship between the use of xylitol, sorbitol, mannitol, maltitol, isomalt, lactitol, HSH, HGS, or a combination of these sugar alcohols and the nonpromotion of dental caries. Thus, it appears that use of a health claim relating the use of sugar-alcohol containing products to dental caries will be useful in helping consumers identify food products consumption of which will not promote the development of dental caries.

A. Xylitol

In its 1978 review of the xylitol studies, FASEB concluded that xylitol appeared to be noncariogenic in studies evaluating the effect of sucrose replacement with xylitol and in studies evaluating the effect of partial replacement of sucrose with xylitol in chewing gum (Ref. 14).

The agency reviewed over 15 studies published since the FASEB report that evaluated the relationship between xylitol and dental caries, plaque pH, and acid production. Overall results from the human caries field trials (Refs. 26 and 28) suggest that substitution of xylitol-containing foods and chewing gums for sucrose-containing foods and chewing gums is associated with a lower incidence of dental caries. Plaque pH and acid production studies further support this result. In both in vivo and in vitro studies, xylitol had negligible to no effect on plaque pH or plaque acid production. In some instances, xylitol increased plaque pH above the mean baseline value, suggesting that xylitol may truly be nonpromotional of dental caries. The results of over 10 animal studies confirm the observations from clinical and in vitro studies. Substituting xylitol (from 10 to 30 percent) for sucrose in a basic laboratory chow resulted in significantly fewer dental caries. FDA tentatively concludes that the overall results from human and animal studies strongly support the observation that xylitol does not promote acid production in plaque and, therefore, does not promote dental caries.

B. Sorbitol

In its 1979 report on sorbitol, FASEB concluded that the weight of evidence from animal studies suggests that sorbitol is less cariogenic than sucrose and other fermentable sugars (Ref. 15). The report noted that the results of human plaque studies show that sorbitol does not lower plaque pH below 5.5, the pH of plaque where decalcification may begin. FASEB concluded that it could be assumed that sorbitol may have similar relative cariogenic properties in humans as observed in animals.

The agency reviewed over 10 clinical studies with sorbitol published since the FASEB report. Subjects consuming sorbitol-containing sweets between meals experienced fewer dental caries than those consuming sucrose-containing sweets. Plaque pH and acid production studies consistently show that sorbitol is slowly fermented by plaque microflora and by *S. mutans* in particular. However, results show that plaque acid did not decrease pH to levels associated with incipient enamel decalcification (i.e., approximately at pH 5.5 or below). There is some evidence that suggests that long-term, uninterrupted use of sorbitol results in adaptation by *S. mutans* and other plaque microorganisms and, therefore, in more acid production. However, there are no human caries trials to show whether such adaptation results in a change in the incidence of dental caries. There is some evidence to show that adaptation may be lost in the presence of other sugars.

The results of six animal studies confirmed the observations from human studies. The incidence of caries in animals consuming diets containing sorbitol was significantly less than the caries incidence in animals consuming diets containing sucrose. FDA tentatively concludes that the overall results from human and animal studies show that oral bacteria cannot be sustained in the presence of sorbitol, and that changes in acidity are within a range that is safe for tooth enamel.

C. Mannitol

In its 1979 report on mannitol, FASEB concluded that results of acid production, plaque pH changes, and changes in microhardness of bovine enamel were consistent with the results of animal experiments indicating that mannitol, in the absence of adaptation of the oral microflora, is less cariogenic than sucrose (Ref. 16). One study evaluated plaque pH with mannitol in a concentrated plaque suspension in vitro (Ref. 38). One and ten percent solutions of mannitol resulted in a plaque pH of 5.5 or below. Contrary to these results, however, three studies showed only slight acid production and small changes in plaque pH to a value not below pH 6.0 from mannitol (Refs. 39, 45, and 76). Likewise, there was little evidence of demineralization from mannitol in vitro (Ref. 76). Two rat studies, in which mannitol was substituted for sucrose in animal chow, showed significantly fewer caries with the mannitol diet (Refs. 59 and 64). FDA tentatively concludes that the overall results from both human and animal studies support the claim that mannitol does not promote dental caries.

D. Maltitol

Results of three ICT's showed significantly less decalcification with maltitol than sucrose. Additional plaque pH studies showed that maltitol is fermented very slowly (acid production of 10 to 30 percent) compared to sucrose and is associated with small plaque pH changes from resting baseline values.

Four animal studies confirmed that maltitol was significantly less cariogenic than sucrose. FDA tentatively concludes that the overall results from both human and animal studies support the claim that maltitol does not promote dental caries.

E. Isomalt

The agency reviewed two plaque pH studies evaluating the acidogenic potential of isomalt. Results with 10 percent isomalt showed a minimum in vitro plaque pH of 5.7. An intraoral test with a 20 percent solution of isomalt reported a minimum pH of about 6.0. Results of five animal studies consistently showed that isomalt was significantly less cariogenic than sucrose. FDA tentatively concludes that the overall results show that isomalt does not lower plaque pH below 5.5 and does not promote dental caries.

F. Lactitol

Two in vitro plaque pH studies showed that lactitol produced little acid and only slight changes in plaque pH from resting baseline values. Results of two animal studies are consistent with these results and showed lactitol to be significantly less cariogenic than sucrose. The cariogenicity of lactitol was not significantly different than xylitol. FDA tentatively concludes that the overall results support the claim that lactitol does not promote dental caries.

G. Hydrogenated Starch Hydrolysates and Hydrogenated Glucose Syrups

In an ICT, a solution of HSH resulted in significantly less demineralization than sucrose. The investigators attributed the observed demineralization with HSH to an effect of other dietary components. The effects of sucrose on enamel demineralization, however, were noted to be over and above the effect of other dietary components.

Seven studies evaluating the effect of HSH on plaque pH showed inconsistent results in final pH values reported. The differences in results are attributed to the source of the HSH. HSH is manufactured by hydrolyzing a source of food grade starch (usually potato or corn starch) with acid or an enzyme to a mixture of sugars and dextrins of various glucose lengths (i.e., glucose syrups). The hydrogenated mixture contains sorbitol, maltitol, maltitriol, maltotrititol, and hydrogenated dextrins of various molecular weights (Ref. 79). The percentage of each component sugar alcohol in the final substance depends on the manufacturing process and controls. The two major forms of HSH (i.e., one manufactured in Sweden and the other in France) used in the studies reviewed gave dramatically different results in plaque pH and acid production tests. The Swedish version, which has a higher percentage of higher molecular weight, fermentable polysaccharides than the French version, produced plaque pH values of 5.5 to 6.0 and an acid production of 50 to 70 percent compared to sucrose. The French version produced final plaque pH values above 6.0 and an acid production rate of 20 to 40 percent of sucrose. Results with HGS of unidentified composition showed minimum plaque pH values all above 6.0. Results of 4 rat studies support the observations that HSH (source not identified) is significantly less cariogenic than sucrose. FDA tentatively concludes that the overall results support the claim that HSH and HGS do not promote dental caries.

Based on its review of the scientific evidence, the agency noted that the HSH and HGS sugar alcohol mixtures may vary in their acidogenic response in dental plaque. For example, HSH manufactured in Sweden usually gave a lower plaque pH response than the French version of HSH. This variation in acidogenic response has been attributed to the differences in the chemical composition of these substances. HSH and HGS are not well defined chemical substances as are xylitol and sorbitol. Instead, the sugar alcohol compositions of these substances will vary depending on the manufacturing process. Therefore, the agency is asking for comments on how to determine whether sugar alcohol mixtures, such as HSH, when used in a food whose label bears a dental caries health claim, are in compliance with any final rule resulting from this proposal.

V. Decision To Propose An Exemption From § 101.14(E)(6) For Chewing Gum and Confectioneries

Section 101.14(e)(6) provides, as stated above, that except for dietary supplements or where provided for in other regulations in part 101, subpart E, to be eligible to bear a health claim, a food must contain 10 percent or more of the reference daily intake or the daily reference value for vitamin A, vitamin C, iron, calcium, protein, or fiber per reference amount customarily consumed before there is any nutrient addition.

The petition states that products containing sugar alcohols often will not be able to satisfy the requirement of § 101.14(e)(6) because the products utilizing sugar alcohols are largely chewing gum and confectioneries, none of which are a significant source of any nutrients. The petition states that the use of these products in lieu of traditional sugar-based confectionery would be consistent with public health recommendations, and that the health claim statement, ''useful only in not promoting tooth decay,'' is an important and useful message for consumers in making decisions on which foods to purchase.

FDA has tentatively determined that there is significant public health evidence to support providing an exemption to § 101.14(e)(6) for sugar alcohol-containing foods, e.g., chewing gums, hard candies, and mints. In the Surgeon General's Report (Ref. 7), dental caries is recognized as an important and widespread public health problem in the United States. Although dental caries among children are declining, the overall prevalence of the condition imposes a substantial economic burden on American health care costs. The Surgeon General's report states that of the 13 leading health problems in the United States, dental disorders rank second in direct costs (Ref. 7).

The role of sugars, and of sucrose in particular, in the etiology of dental caries is well established. Caries-producing bacteria can readily metabolize a range of simple sugars (e.g., sucrose, glucose, fructose) to acids that can demineralize teeth. The unique role of sucrose, however, is related to its ability to be used by *S. mutans*, the primary etiologic agent in coronal caries, and other oral bacteria to form extracellular polymers of glucose or fructose that adhere firmly to tooth surfaces (Ref. 7).

The Surgeon General's report recommends several types of intervention to help reduce the risk of dental caries. The diet-related factors include the use of fluoridated drinking water and control of sugars consumption. In this regard, the Surgeon General's report recommends that those who are particularly vulnerable to dental caries, especially children, should limit their consumption and frequency of use of foods containing relatively high levels of sugars.

FDA agrees that limiting the amount of sugars in the diet is one important approach to help reduce the risk of dental caries. Sugar alcohols can be used to replace dietary sugars in food by providing sweetness and usefulness as bulking agents. Sugar alcohol-containing chewing gum and confectioneries, such as hard candies and mints, are specifically formulated without dietary sugars. Although these foods have little or no nutritional value,

they are an important alternative to sucrose-containing snacks. Therefore, FDA tentatively finds that the use of health claims on the label of sugar alcohol-containing products will facilitate compliance with dietary guidelines that recommend a reduced intake of dietary sugars to reduce the risk of dental caries. Moreover, the sugar alcohol and dental caries health claim, if authorized, will apply in large measure, although not entirely, to snack foods that do not play a fundamental role in structuring a healthy diet.

Section 101.14(e)(6) was included in FDA's regulations to ensure that those foods that bear a health claim are useful in structuring a healthy diet. Usually usefulness in structuring a healthy diet derives from the vitamin, mineral, protein, or fiber content of the food. In this case, however, FDA tentatively finds that the replacement of dietary sugars with sugar alcohols will help reduce the risk of dental caries and thus will help to facilitate compliance with the dietary guidelines. In recognition of the special character of the foods involved, FDA tentatively concludes that it is appropriate to exempt these food products from § 101.14(e)(6). Therefore, in new § 101.80(c)(1), FDA is proposing to exempt sugar alcohol-containing food products from the provisions of paragraph 101.14(e)(6).

VI. Description And Rationale For Components Of Health Claim

A. Relationship Between Sugar Alcohols and Dental Caries

In proposed § 101.80(a), FDA describes the relationship between sugar alcohols and dental caries. Dental caries is a multifactorial disease, characterized by the demineralization of the surface of tooth enamel by acid-forming organisms in dental plaque. It is well established that the relationship between sugars consumption and dental caries is one of cause and effect within the multifactorial context (Refs. 71 and 72). The role of sucrose in the etiology of dental caries is related to its ability to be metabolized by oral bacteria into extracellular polymers that adhere firmly to the tooth surfaces, at the same time forming acids that can demineralize tooth enamel (Ref. 7). The extracellular polymers that adhere to tooth surfaces (i.e., plaque) facilitate the further attachment of additional plaque to teeth and the proliferation of bacteria. Although saliva can help neutralize plaque acids and influence the attachment of oral bacteria to the tooth surface (Ref. 7), it has limited access to the acids generated at the tooth surface beneath the plaque.

Diets in the United States tend to be high in sugars. Although there has been a decline in the prevalence of dental caries in the United States, there has been no decline in the consumption of sugars. Furthermore, the incidence of dental caries is still widespread (Ref. 7).

Sugar alcohols are used as sweeteners and bulking agents to replace dietary sugars in foods. Because of their composition, sugar alcohols are not as fermentable by plaque bacteria as sucrose and are, therefore, less cariogenic than dietary sugars. Replacing dietary sugars with sugar alcohols helps to maintain dental health.

B. Significance of Sugar Alcohols in the Caries Process

As explained in section IV of this document, based on the totality of the publicly available evidence, FDA has tentatively concluded that there is significant scientific agreement among experts qualified by training and experience to evaluate such claims that there is adequate scientific evidence to conclude that the sugar alcohols xylitol, sorbitol, mannitol, maltitol, isomalt, lactitol, HSH, and HGS are less cariogenic than sucrose and do not promote dental caries. In proposed § 101.80(b), FDA discusses the significance of the relationship between sugar alcohols and dental caries.

Sugar alcohols have been shown in human and animal studies to be nonfermentable (i.e., xylitol) or slowly fermentable (i.e., sorbitol, maltitol, mannitol, isomalt, lactitol, HSH, and HGS) by *S. mutans* and other acid-forming microorganisms in dental plaque. Human studies have shown a reduced rate of acid production in plaque and, in some studies, a reduced incidence of dental caries from the use of sugar alcohol-containing products.

C. Nature of the Claim

In new § 101.80(c)(1), FDA is proposing that all requirements of § 101.14 be met except, as explained above, that sugar alcohol-containing foods are exempt from § 101.14(e)(6).

Under § 101.14(d)(3), nutrition labeling in accordance with § 101.9 must be provided on the label or labeling of any food for which a health claim is made. Therefore, if FDA adopts this proposed regulation, the labeling of the amount of sugar alcohol in a serving will have to be declared on the nutrition label in accordance with § 101.9(c)(6)(iii) when a claim is made on the label or in labeling about sugar alcohols and dental caries.

In new § 101.80(c)(2)(i), FDA is proposing to authorize a health claim on the relationship between sugar alcohols and the nonpromotion of dental caries. This action is consistent with the agency's review of the scientific evidence, which showed that, although sugar alcohols are slowly fermented by *S. mutans* and can form some acid, they do not contribute to the promotion of dental caries.

In new § 101.80(c)(2)(i)(A), the agency is proposing to require that in describing the relationship between sugar alcohols and dental caries, the claim states ''does not promote,'' ''useful in not promoting,'' or ''expressly for not promoting'' dental caries. FDA finds that these terms accurately describe the relationship between sugar alcohol consumption and dental caries.

In new § 101.80(c)(2)(i)(B), the agency is proposing to require that the terms ''dental caries'' or ''tooth decay'' be used in specifying the disease. These terms are commonly used in dental and dietary guidance materials and are familiar to consumers.

Under § 101.14(d), a health claim must be complete, truthful, and not misleading. It must enable the public to comprehend the information provided and to understand the relative significance of such information in the context of a total daily diet. In addition, a health claim may not attribute any specific degree of reduction in risk of disease from consumption of the product.

In recognition of these general requirements, and in light of the fact that both environmental and genetic factors, as well as eating behaviors, all affect a person's risk of developing dental caries (see proposed § 101.80(a)(1)), FDA is proposing in § 101.80(c)(2)(i)(C) that for packages that have a total surface area available for labeling of 15 or more square inches, the claim must state that dental caries depends on many factors.

FDA is aware that many sugar alcohol-containing chewing gum and confectionery products have a total surface area available for labeling of less than 15 square inches, however. Such a small area would preclude the use of a health claim that included all of the required elements. Many of these products, packaged in small packages, have used the claim ''useful only in not promoting dental caries'' on their labels for more than 15 years. Because of the potential dental health benefits to consumers resulting from a positive action on this proposal and given the unique history of this claim, the agency tentatively finds that continued use of an abbreviated claim on packages with less than 15 square inches of surface area will not be misleading or confusing

to consumers of these products. However, the agency continues to believe that the fact that dental caries are multifactorial in their etiology is fundamental to an understanding of the claim. Therefore, the agency tentatively concludes that this fact is a material fact, and that it must be disclosed on packages with space available for labeling of 15 or more square inches. In § 101.80(c)(2)(i)(D), given the unique circumstances surrounding this claim, FDA is proposing to exempt packages with a total surface area available for labeling of less than 15 square inches from the provisions of § 101.80(c)(2)(i)(C).

In proposed § 101.80(c)(2)(i)(E), FDA states that the claim must not attribute any degree of nonpromotion of dental caries to the use of the sugar alcohol-containing food. Based on the agency's review of human and animal studies in this document, none of the studies provide a basis for determining the percent reduction in risk of dental caries from consuming sugar alcohol-containing foods. This requirement is also consistent with the general requirements for health claims in § 101.14(d), and those health claims authorized under part 101, subpart E.

D. Nature of the Food

In § 101.80(c)(2)(ii)(A), FDA is proposing to require that the food bearing this health claim meet the requirement in § 101.60(c)(1)(i) with respect to sugars content, that is, qualify to bear the claim ''sugar free.'' This requirement is consistent with the scientific evidence showing that foods with a mixture of sugar alcohols and sugars are still acidogenic (Ref. 38) and cariogenic (Refs. 52, 55, and 56, for examples).

In new § 101.80(c)(2)(ii)(B), the agency is proposing that the sugar alcohols be limited to xylitol, sorbitol, mannitol, maltitol, isomalt, lactitol, HSH, HGS, or a combination of these. This requirement reflects the available scientific evidence on the sugar alcohols and their effects on the promotion of dental caries.

Sugar alcohols in combination with high intensity sugar substitutes, such as aspartame and saccharin, are also used to replace sucrose. The agency notes that under proposed § 101.80(c)(2)(ii)(A) and (c)(2)(ii)(B), a sugar alcohol and dental caries claim could appear on a food that contains a combination of sugar alcohols and high intensity sweeteners but no sugars. The agency notes that high intensity sweeteners are not considered fermentable by oral bacteria (Ref. 75).

The agency is not specifying a level of sugar alcohols in the food product because these ingredients are being used as a substitute for sugars. Therefore, the amount of the substance required is that needed to achieve a desired level of sweetness.

In new § 101.80(c)(2)(ii)(C), the agency is proposing that to qualify to bear a claim, the sugar alcohol-containing food, when tested for its effects on plaque pH using in vivo methods, must not lower plaque pH below 5.7. Based on the agency's review of the scientific evidence, foods that lowered plaque pH below 5.5 were contributing to an acidic environment in the mouth that is detrimental to tooth enamel. Although a ''critical'' plaque pH has not been defined, changes in pH to a minimum that is above 5.5 are generally considered above the level where enamel decalcification would be promoted (Refs. 8, 75, 86, and 87).

In its review of the scientific evidence, the agency noted that sugar alcohol-containing chewing gum and confectioneries, such as mints, that do not contain fermentable carbohydrates, did not lower plaque pH below 5.5. However, in one study that evaluated the cariogenic potential of an experimental licorice that contained soy flour, the soy flour was shown to be highly fermentable and dropped plaque pH to below 5.5 (Ref. 43). The agency is concerned that use of sugar alcohols in a food product that contains an ingredient, such as refined flour, that would cause plaque pH to drop below 5.5 would thus cause the food to be cariogenic.

In the Swiss ''zahnschonend'' program, if a food does not promote a drop in plaque pH, using intraoral plaque pH telemetric tests, below 5.7 by bacterial fermentation either during consumption or up to 30 min later, the food is considered ''safe for teeth'' and may be labeled as such (Ref. 75). The intraoral plaque pH telemetric test is an in vivo method that measures the acidogenicity of foods and dietary patterns. Based on experience and experimentation, foods judged by the Swiss program to be safe for teeth are those that have been shown not to promote dental decay in animal or human model systems (Ref. 75).

In this proposed rule, FDA is proposing to require in § 101.80(c)(2)(ii)(C) that to be eligible to bear the claim, the food product not lower plaque pH below 5.7, based on in vivo measurements, during the time food is consumed and for up to 30 min after the food is consumed. The agency is proposing a more conservative value than pH 5.5 because such a value gives assurance that, consistent with the health claim, the food will not promote dental caries.

The methods that have been described as the most suitable for assessing plaque acidity of dietary constituents in humans are indwelling electrode systems, such as the intraoral plaque pH telemetric test used in the Swiss program (Refs. 8 and 75). ICT's (Ref. 88), which incorporate enamel blocks into dental appliances for the production of carious lesions when used in combination with intraoral plaque pH telemetry, are also good methods for assessing changes in plaque pH in response to food. The agency is asking for comments on whether establishing a minimum plaque pH that is measured in vivo during consumption and up to 30 min following consumption is a reasonable approach to use to determine whether a sugar alcohol-containing food, other than sugar alcohol-containing chewing gum and confectioneries, that contains other carbohydrate ingredients is in compliance with any final rule resulting from this proposal.

E. Optional Information

FDA is proposing in new § 101.80(d)(1), consistent with the regulations that have authorized other health claims, that health claims about the relationship between sugar alcohols and dental caries may provide additional information that is drawn from proposed § 101.80 (a) and (b).

In new § 101.80(d)(2), the agency is proposing that when referring to sucrose, the claim may use the term ''sucrose'' or ''sugar.'' The use of either of these terms is consistent with FDA's regulation that affirms that use of this substance is GRAS (§ 184.1854).

FDA is proposing in § 101.80(d)(3), consistent with the health claims that it has already authorized under part 101, subpart E, to allow manufacturers to provide additional information about risk factors associated with the development of dental caries. Although sugars consumption and infection with *S. mutans* are often identified as the cause of dental caries, there are several risk factors that play significant roles in the etiology of this disease (Ref. 71). These factors include frequent consumption of sucrose or other fermentable carbohydrates, presence of oral bacteria capable of fermenting sugars, length of time sugars are in contact with the teeth, lack of exposure to fluoride, individual susceptibility, socioeconomic and cultural factors, and characteristics of tooth enamel, saliva, and plaque (Refs. 7, 71, and 89).

F. Model Health Claims

In proposed § 101.80(e), FDA is providing model health claims to illustrate the requirements of new § 101.80. FDA emphasizes that these model health claims are illustrative only. If the agency authorizes claims about the relationship between sugar alcohols and dental caries, manufacturers will be free to design their own claim so long as it is consistent with § 101.80(c).

VII. Environmental Impact

The agency has determined under 21 CFR 25.24 (a)(11) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because it enables firms to make claims that they would otherwise be prohibited from making, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

IX. Effective Date

FDA is proposing to make these regulations effective 30 days after the publication of a final rule based on this proposal.

X. Comments

Interested persons may, on or before October 3, 1995, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

XI. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a. m. and 4 p. m., Monday through Friday.

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List of Subjects in 21 CFR Part 101

Food labeling, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 101 be amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 is revised to read as follows:

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 371).

2. New § 101.80 is added to subpart E to read as follows:

§ 101.80 Health claims: dietary sugar alcohols and dental caries.

(a) *Relationship between dietary sugar alcohols and dental caries.* (1) Dental caries, or tooth decay, is a disease caused by many factors. Both environmental and genetic factors can affect the development of dental caries. Risk factors include tooth enamel crystal structure and mineral content, plaque quantity and quality, saliva quantity and quality, individual immune response, types and physical characteristics of foods consumed, eating behaviors, presence of acid producing oral bacteria, and cultural influences.

(2) The relationship between dietary sugars consumption and tooth decay is well established. Sucrose is one of the most, but not the only, cariogenic sugar in the diet. Bacteria found in the mouth are able to metabolize sugars producing acid and forming dental plaque. Prolonged exposure of the tooth enamel to acids from dental plaque causes tooth enamel to demineralize, or decay. Frequent between-meal consumption of sugary foods, particularly foods that easily stick to the teeth, can cause tooth decay.

(3) U.S. diets tend to be high in sugars consumption. Although there has been a decline in the prevalence of dental caries in the United States, per capita consumption of sugars has not declined, and the disease remains widespread throughout the population. Federal government agencies and nationally recognized health professional organizations recommend decreased consumption of sugars.

(4) Dietary sugar alcohols can be used to replace dietary sugars in food. Sugar alcohols are significantly less cariogenic than dietary sugars. Thus, replacing dietary sugars with sugar alcohols helps to maintain dental health.

(b) *Significance of the relationship between sugar alcohols and dental caries.* Sugar alcohols do not promote

dental caries because they are slowly metabolized by bacteria to form some acid. The rate and amount of acid production is significantly less than that from sucrose and does not cause the loss of important minerals from tooth enamel.

(c) *Requirements.* (1) All requirements set forth in § 101.14 shall be met, except that sugar alcohol-containing foods are exempt from section § 101.14(e)(6).

(2) Specific requirements. (i) *Nature of the claim.* A health claim relating sugar alcohols and the nonpromotion of dental caries may be made on the label or labeling of a food described in (c)(2)(ii) of this section, provided that:

(A) The claim shall state ''does not promote,'' ''useful in not promoting,'' or ''expressly for not promoting'' dental caries.

(B) In specifying the disease, the claim uses the following terms: ''dental caries'' or ''tooth decay.''

(C) For packages with a total surface area available for labeling of 15 or more square inches, the claim shall indicate that dental caries depends on many factors.

(D) Packages with a total surface area available for labeling of less than 15 square inches are exempt from paragraph (C) of this section.

(E) The claim shall not attribute any degree of nonpromotion of dental caries to the use of the sugar alcohol-containing food.

(ii) *Nature of the food.* (A) The food shall meet the requirement in § 101.60(c)(1)(i) with respect to sugars content.

(B) The sugar alcohol in the food shall be xylitol, sorbitol, mannitol, maltitol, isomalt, lactitol, hydrogenated starch hydrolysates, hydrogenated glucose syrups, or a combination of these.

(C) The sugar alcohol-containing food shall not lower plaque pH below 5.7 by bacterial fermentation either during consumption or up to 30 minutes after consumption, as measured by in vivo tests.

(d) *Optional information.* (1) The claim may include information from paragraphs (a) and (b) of this section, which describe the relationship between diets containing sugar alcohols and dental caries.

(2) In referring to sucrose, the claim may use the term ''sucrose'' or ''sugar.''

(3) The claim may identify one or more of the following risk factors for dental caries: Frequent consumption of sucrose or other fermentable carbohydrates; presence of oral bacteria capable of fermenting sugars; length of time sugars are in contact with the teeth; lack of exposure to fluoride; individual susceptibility; socioeconomic and cultural factors; and characteristics of tooth enamel, saliva, and plaque.

(e) *Model health claim.* The following model health claims may be used in food labeling to describe the relationship between sugar alcohol and dental caries.

(1) For packages with total surface area available for labeling of less than 15 square inches:

(i) Useful only in not promoting tooth decay;

(ii) Does not promote tooth decay; and

(iii) [This product] does not promote tooth decay.

(2) For packages with total surface area available for labeling of 15 or more square inches:

(i) Tooth decay is a disease caused by many factors including frequent between meal consumption of sugary foods. [Name of sugar alcohol] does not promote tooth decay.

(ii) [Reserved].

Dated: July 7, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

Note: The following tables will not appear in the annual Code of Federal Regulations.

BILLING CODE 4160–01–P

Table 1.-- Sugar Alcohols and Plaque pH, Acid Production

Study	Study Design	Subjects	Methods	Results	Comments
Bibby and Fu, 1985 (Ref. 38)	Study to evaluate in vitro method for determining plaque pH	Adult volunteers	Fresh plaque was collected from adult volunteers who had suspended oral hygiene for 24 to 48 hours (hr) and who had not eaten for 2 hr prior to plaque removal. Plaque was connected to pH meter and strip chart recorder. Methods described in detail in the study. Sweeteners used were: HSH (mostly SOR), SOR, MANN, isomaltulose, ISO, sorbose, X, saccharine (SACC), and aspartame (ASP). All but SACC and ASP were prepared as 0.1, 1.0, and 10% aqueous solutions. SACC and ASP were diluted in water to give sweetness equivalents of 0.1, 1.0 and 10% S solutions. Experiment 1: Plaque responses to SOR, MANN, X were compared to S, F, maltose, raffinose, and corn starch. Exp. 2: other sweeteners were used.	Plaque pH in presence of sugar alcohols after 20 min of incubation Soln Conc (w/v) Substrate / 0.1% / 1.0% / 10% Sucrose 5.42 4.82 4.15 Fructose 5.47 4.39 4.14 Maltose 5.24 4.53 4.22 Raffinose 5.75 5.03 4.30 Mannitol 5.67 5.54 5.22 Sorbitol 6.30 6.17 5.82 Xylitol 6.07 6.13 6.13 Corn starch 5.55 4.85 4.29 Mean pH of plaque after incubation for 20 min with solutions up to 10% of isomaltulose resulted in a low pH similar to that of S. Increasing concentrations of ISO and HSH resulted in lowered pH of plaque compared to the pH in the 0.1% solution of the sweetener. The lowest pH values reported were about 5.6 (ISO) and 5.0 (HSH). Results of incubation of plaque with both S and X showed that X did not interfere with S fermentation.	The 10% solution of HSH resulted in a final plaque pH that is detrimental to dental enamel. Authors state that the HSH was mainly SOR. The results showing that plaque pH increases with increasing concentration of X, while the pH of all the other sugars tested decreased, provides support for the contention that X is nonpromotional for caries. For SOR, MANN, HSH, and ISO, the trend towards decreasing pH with increasing concentration, suggests that at a slightly higher concentration (>10%), the pH might dip below the level required for demineralization of enamel (pH 5.5).

Table 1.-- Sugar Alcohols and Plaque pH, Acid Production

Study	Study Design	Subjects	Methods	Results	Comments
Birkhed et al., 1978 (Ref. 40)	In vitro study of acid production from GLU and SOR in dental plaque suspensions and in vivo pH changes after mouth rinses	18 subjects, 25-40 years old	Prior to study, all Ss used SOR dentifrices and consumed sporadically SOR-containing products (gums, candies). No oral hygiene 2 (d) before; no professional cleaning before this 2-day period. Plaque was scraped off buccal, lingual, and approximal surfaces. Methods for measuring acid production are described in the study. After acid production was followed for 6 min, 1 mL of 0.2 M GLU solution control (C) was added and acid production was followed for another 6 min. This procedure was repeated using SOR as a substrate. One week after acid measured, Ss rinsed with water, then rinsed for 30 sec with 10% GLU soln. Sample plaque was taken immediately and at time 2, 5, 10, 20 and 30 min after the rinse. Analysis carried out using the pH values or the differences between pH values. Paired t-test used for statistical analysis. Adaptation period: Ss also instructed to rinse 6 x per day for 6 weeks with a 10% SOR soln without swallowing it. After 4 weeks, plaque was collected for determination in vitro acid production and after 5 and 6 weeks of adaptation, plaque pH in vivo was measured after mouth rinses with GLU and SOR.	Results showed acid production with SOR before the SOR adaptation period was 11.3% of that resulting from the GLU control. After the adaptation period, acid production from SOR increased to 30.4%, a significant increase ($p<0.001$) from the before adaptation period. Mean plaque pH with 10% GLU soln before (B) and after (A) SOR adaptation pH 0: B 6.77, A 7.04, (p) <0.01 2: B 6.06, A 6.25, (p) <0.05 5: B 5.88, A 6.11, (p) <0.05 10: B 5.77, A 5.98, (p) - 20: B 6.25, A 6.38, (p) - 30: B 6.55, A 6.66, (p) - Mean plaque pH with 10% SOR soln before and after SOR adaptation pH 0: B 6.91, A 7.07, (p) - 2: B 6.96, A 6.94, (p) - 5: B 7.01, A 6.83, (p) - 10: B 6.99, A 6.76, (p) <0.05 20: B 7.00, A 6.67, (p) <0.01 30: B 6.99, A 6.86, (p) - Significant difference between time (t) 0 and t = 10 and between t = 0 and t = 20, $p<0.01$; and t = 0 and t = 30, $p<0.05$.	Authors state that increased in vitro acid production from SOR after the adaptation period shows that adaptation occurred. Authors note that initial plaque pH values in the presence of GLU were a little higher after adaptation than before and these differences may have influenced statistical analyses of pH differences. However, pH curves for GLU before and after adaptation ran almost parallel to each other, whereas the SOR curves did not. SOR pH values after adaptation decreased slightly over 30 min, although differences were significant at 10 and 20 min. Authors conclude that these experiments suggest that the fermentability of SOR was more pronounced after adaptation than before. They also conclude that SOR can be regarded as a satisfactory low-cariogenic substitute for fermentable sugars, such as S, fructose and GLU.

Table 1.-- Sugar Alcohols and Plaque pH, Acid Production

Study	Study Design	Subjects	Methods	Results	Comments
Birkhed et al., 1978 (Ref. 41)	Intervention to study effects on in vivo pH and in vitro acid production from HSH (Swedish HSH), MALT, SOR, X. Randomized, blinded.	110 men and women (68 men, 42 women), ages 19 to 58 years.	3-month study. Ss divided into 4 groups and instructed to suck on 2 lozenges, 4 times a day between meals. Each lozenge contained 0.5 g of sweetener and 0.5 g gum arabic. No other dietary instructions were given. Changes in in vivo pH were measured after a mouth rinse for 30 sec with 10 mL of 50% soln of HSH, MALT, SOR, or X. The rinse was used 1 week before and 1 week after lozenge-consumption period. A no lozenge control group also rinsed with one of the four soln as did the test groups. Control (C) group had no diet or candy restriction during the 3-month test period. Plaque acid production activities were measured in vitro 1 week before and after the 3-month test period. Student's t-test and two-way analysis of variance used on plaque pH values of 5 groups.	Before the test period, the pH of HSH showed its lowest value at 10 min. Plaque pH values, after test, were similar, but all pH values were lower. Differences in pH values before and after testing were not statis. significant. The lowest pH values attained were above pH 6.0. Results of acid production measures showed HSH at 56-59%, compared to GLU (100%). MALT slightly raised pH from baseline to the highest value at 2 min (before and after). After the test period, pH values were lower than before, and pH differences 0-2 min, 0-10 min, and 0-30 min before compared with after the test period were statis. signif. ($p<0.05$). The lowest pH reported was about 6.8. Acid production, compared to GLU, was 26 and 32%. SOR raised pH values above baseline before test period. After test period, all pH values were lower than before but remained above 6.0. pH changes 0-20 and 0-30 min before compared to after the test period were statistically significant ($p<0.05$). Acid production, compared to GLU, was 15 and 18%. X increased pH before the test period. There was no significant difference in the pH before and after the test. No acid production reported for X compared to GLU. In C group, X and MALT gave similar pH curves. The SOR curve showed an initial rise and then slight lowering to almost horizonal. HSH caused the lowest pH values.	The control group was not controlled for intake of sugar alcohols during the 3-month study period. This group was tested with GLU and not S. Authors state that HSH does not cause as large pH changes as S. It would have been helpful to have had a S group. Authors state that it may be incorrect to conclude that HSH (Swedish HSH) is non-cariogenic, since it contains high molecular weight hydrogenated saccharides from which fermentable low molecular weight sugars are set free on contact with salivary amylase.

Table 1.-- Sugar Alcohols and Plaque pH, Acid Production

Study	Study Design	Subjects	Methods	Results	Comments
Birkhed and Edwardsson, 1978 (Ref. 39)	In vitro study to evaluate the effects of various S substitutes on acid production in individual plaque samples	Not given	Subjects (Ss) instructed not to clean teeth for 2 days (d) before experiment and not to eat or drink anything the morning of the exam. On day 3, Ss rinsed with distilled water for 10 seconds (sec) before plaque was removed from the buccal, lingual, and approximal surfaces of the teeth. Plaque treatment is described in the study. 1 mL of 0.2M glucose (GLU) soln was added to plaque suspension and acid production was followed for 10 minutes (min). Repeated acid production experiments performed with 1 mL of substrates: MANN, X, MALT, SOR, French HSH, lactose, Swedish HSH, fructose, GLU syrups. Plaque pH was also determined. Ss rinsed with distilled water, plaque was collected and pH measured (time 0). Ss rinsed for 30 sec with 10 mL concentrated soln of GLU or S. Plaque again taken and pH determined at 2, 5, 10, 20, and 30 minutes (min) after the rinse. Mouth rinses repeated at 1 week intervals with the test substances. Student's t-test for paired observations used when comparing fermentability of various substrates and when measuring pH	**Acid Production Rates** **Substrates** — **Percent** MANN, X — 0 MALT, SOR — 10-30 French HSH — 20-40 Lactose — 40-60 Swedish HSH — 50-70 Fructose — 80-100 Glucose syrups — 100 Results of pH measurements showed that X, MALT, MANN, and French HSH increased or in some cases only slightly decreased plaque pH (pH remaining about 6.8 to 7.0). SOR showed a slight decrease in pH but the pH remained about pH 6.7 to 6.8. Swedish HSH decreased pH to just below 6.0 after 5 min. The pH increased to over 6.0 after 30 min. Lowest plaque pH in S and fructose was about 5.5 or below.	Authors report error of method to measure acid production has been calculated to be 10-15% in duplicate experiments with GLU. French HSH is said to contain fewer high moleculer weight hydrogenated polysaccharides than Swedish HSH and, therefore, is less fermentable. Authors note that lower pH values are obtained if the pH of interoral plaque is measured. It is also noted that pH methodology used in this study does not give information of the pH at any particular site of a tooth, rather it gives overall averages.
Birkhed and Skude, 1978 (Ref. 51)	In vitro study to compare acid production from HSH and soluble starch	11 adult subjects	Subjects were instructed to avoid oral hygienic procedures for 2 d. Ss rinsed with tap water; dental plaque was then removed. Acid production activities (APA) from 3% GLU solutions, boiled soluble starch, and Swedish HSH were determined in 0.1 mL samples of dental plaque. In a separate experiment (Ss n=4) APA was determined in 1 concentrations (0.003 to 12% w/v) of Swedish HSH and starch. Student's paired t-test for comparison between APA was used.	**APA expressed as a % of that from GLU (mean values)** **%** **GLU** — 99.7 **Starch** — 75.7 **HSH** — 61.5 APA from soluble starch and HSH was optimal at a substrate concentration of 0.03 - 6%.	Authors note that Swedish HSH is more fermentable than HSH 80/55 made in France. Compared to GLU, Swedish HSH is very fermentable, although the rate is slower. Results of this study raise questions regarding the usefulness of Swedish HSH in dental health.

Table 1.-- Sugar Alcohols and Plaque pH, Acid Production

Study	Study Design	Subjects	Methods	Results	Comments
Frostell, 1969 (Ref. 42)	In vitro study to evaluate the effect of different physical and chemical factors on pH changes in dental plaque after intake of sugar solutions and different types of candy and foods.	41 Ss, ages 15-50 years, with average to high dental caries activity	Groups with either 18, 13, or 10 Ss. Ss told not to brush their teeth 2 (d) before the experiment and not to eat or drink on the day of the experiment. Plaque was collected and pooled: pH was determined immediately. Ss then rinsed mouths for 30 sec with 10 mL of test solution or ate food being tested. After 2, 5, 10, 20, and 30 min, new samples of plaque were taken and pH determined. Statistical evaluation performed on differences in pH at a certain time and baseline. Rinses tested: S (0.05% to 50% soln.) Foods: SOR tablets (45%), sugar tablets (GLU plus S, 45%), HSH candy (97%), conventional candy (S, 55%; dextrose and maltose, 18%), marmalade (60%), and sponge cakes, ginger cakes, marshmallows, and chocolates (some with 45% S and others S free).	Increasing concentrations of S resulted in ↓ pH. pH dropped rapidly below pH 6 within 5 min for the 5% and 50% soln. Plaque pH after 30 min for the 50% soln remained below pH 6. SOR tablets: Ss consumed 2 tablets. Results showed SOR ↑ plaq pH to about 6.8 within first 5 min followed by a return to baseline (about pH 6.5). S tablets resulted in pH drop to about 6.0 within first 5 min, followed by a return to about pH 6.3. HSH candy: Results showed only slight ↓ (0.26 units) in plaque pH from about pH 6.6 to about pH 6.3; S from lozenges resulted in a ↓ to about 5.8. A S solution produced a minimum pH of about 5.3. HSH in marmalade: pH ↓ from 7.0 to 6.0 after 5 min followed by ↑ to about 6.5. S marmalade: pH ↓ to 5.3. After 30 min pH ↑ to 6.0.	Length of study not mentioned. Methods do not indicate if the Ss consumed the food and candy or rinsed with solutions once or over a period of time before collecting plaque. No mention of Ss dietary intakes or other sweeteners consumed prior to study. Actual baseline pH not given except as shown on graphs. Small number of subjects in HSH experiment. This study did not focus on the effect of sugar alcohols on plaque pH, rather it was to evaluate other carbohydrates. Statistical significance was not reported.
Gallagher and Fussell, 1979 (Ref. 44)	In vitro study to compare fermentability of X with other sugars in dental plaque	50 plaque donors from people of European and Polynesian origin: Group A - 25 adult workers in health fields Group B - 13 adult dental patients Group C - 12 children attending school dental clinic Subgroups were formed under Groups A and C to include individuals of similar dietary habits.	Plaque was collected from lingual surfaces of 1 or 2 teeth per subject. Control media contained no added carbohydrate. Test broths contained 1% arabinitol, X, ribitol, or S. After incubation plaque samples, acid production was measured as pH. 2 Ss in group A wore intraoral caries dentures. The dentures were worn continuously for 5 (d) except for 6 or 7 daily test periods of 15 min., when it was removed and one enamel block was exposed to 5% X soln. Plaque was collected at end of 5 (d). Plaque was plated to determine the presence of X fermenters.	Mean pH of sugars control media / X media / S media / ANOVA Group Ss A 1-10: 6.35 / 6.36 / - / A 11-14: 6.26 / 6.10 / - / A 15-25: 6.17 / 6.26 / 4.69 / * B 26-38: 6.71 / 6.59 / 4.23 / ** C1 39-46: 6.38 / 6.26 / ***4.28 / NS C2 47-50: 6.33 / 6.01 / 4.31 / * * probably signif. p<0.05 ** signif. p<0.01 *** highly signif p<0.001	X was shown to be significantly less acidogenic compared to S.

Table 1.-- Sugar Alcohols and Plaque pH, Acid Production

Study	Study Design	Subjects	Methods	Results	Comments
Gehring and Hufnagel, 1983 (Ref. 45)	Study to describe 2 intra- and extraoral measurements of plaque pH.	6 male or female Ss, ages 19-31 years	Intraoral pH measurements of dental plaque were performed with a modified surface glass electrode. Extraoral pH was measured on dental plaque using a single rod measurement chain with a flat membrane. Test substances: S, fructose, HSH, MANN, ISO, SOR, X, sorbose: 20% soln in water and used as a rinse. Baseline pH: Ss chewed paraffin for 5 min pH then measured. Ss rinse for 2 min with test soln then plaque pH was measured intraorally over a 32 min time period. Visible plaque was removed for extra-oral measurements of pH over a 25 min time period after mouth rinsing with test substances.	Baseline pH between 6.5 and 7.0. Intraoral Within 5 min, S and fructose showed a plaque pH ↓ to below pH 5.0. By 32 min, pH ↑ to between 5.0 and 5.5. Plaque pH for SOR showed the lowest pH after 5 min with a value of about 6.0. HSH resulted in a ↑ in pH to between 5.5 and 6.0 after 7 min X showed only a slight ↑ in pH to a value between 6.3 and 6.5. MANN showed a small ↑ in pH to about 6.2-6.3. ISO showed a maximum plaque pH ↑ to about 6.0. Over the 32 min test period, the pH of each of these substances slowly increased. Extraoral S and fructose showed similar pH decreases as measured intra-orally but the minimum pH were between 5.0 and 6.0. No other pH values given.	X had the least effect on plaque pH intra-orally. MANN and SOR showed similar decreases in pH to 6.0 - 6.3. HSH and ISO showed some pH drop to 6.0 or slightly below.
Grenby et al., 1989 (Ref. 76)	In vitro study to compare dental properties of Lac with five other sweeteners	plaque microorganisms were collected from panel of volunteers	LAC, GLU, S, SOR, MANN, and X in 1% solutions were made in sterile 1% peptone-F media. Plaque was incubated, 24 hr, in media with sweetener with standard segments of intact surfaces of extracted human molar teeth. At the start and finish of incubation and at 30- and 60-min intervals during the first 7 hr, pH, and total acid were measured. Polysaccharide synthesis was also measured. t-tests or F-test used to evaluate differences.	Acid development: GLU > S > MANN and SOR > Lac > X Final pH: S and GLU: 4.0 - 4.3 MANN and SOR: 4.6 - 5.1* LAC and X: 6.1 - 6.3* *Significantly less acid and higher pH than from S and GLU Significantly less polysaccharide synthesis was found in the polyols compared to S and GLU. No signif. difference between S and GLU. X had significantly less polysaccharide development than all the other sweeteners.	X and Lac showed little acid production and change in pH. SOR and MANN showed slight changes in acid production and plaque pH over the first 12 hr, followed by further pH decrease under the conditions of this experiment.
Havenaar et al., 1978 (Ref. 46)	In vitro study to evaluate acid formation in growing cultures by oral bacteria.	Caries-free and caries active subjects were used to obtain fresh isolates of Streptococci and Actinomyces strains.	Sugar substitutes used: SOR, X, LAC, MALT, sorbose and HSH. Micro-titer plates were filled with phenol red broth with addition of 1% GLU or sugar substitute, agar, and inoculated with bacterial suspension without carbohydrate. After 72 hr, a color change indicated acid formation. pH was measured. The growth of S. mutans was measured in GLU broth with or without added X, pH was measured.	No acid production from X. S. mutans produced acid from MALT, SOR, LAC and HSH. Actinomyces species were able to ferment SOR, LAC, and HSH. Fermentation results showed no change in pH from X and a pH ↑ to between 6.0 to about 6.5 with LAC, HSH, MALT, and SOR over a 120-min test period. Testing with S. mutans strain adapted to sugar alcohols showed no pH changes with X, but marked increased fermentation with MALT, HSH, SOR, and LAC. Minimum plaque pH values reported were between 5.0 and 6.0. Adaptation was lost after subculturing once in GLU.	in vitro fermentation by oral microbes was shown with all sugar substitutes except X. Authors state that S. mutans slowly fermented the other sugar alcohols. Adaptation to sugar alcohols by oral microflora was quickly lost.

Table 1.-- Sugar Alcohols and Plaque pH, Acid Production

Study	Study Design	Subjects	Methods	Results	Comments
Jensen, unpublished (Ref. 47)	In vivo study of interproximal plaque pH using HSH compared to SOR and S	4 adults, ages 24 to 38	A removable telemetric appliance was constructed which contained a glass pH microelectrode. The appliance was placed interproximally and plaque accumulated for 3 day prior to first test. Resting pH measured. Ss rinsed with test substance for 60 sec Plaque pH monitored for 30 min at which time Ss rinsed with distilled water. Paraffin was chewed for 5 min to restore resting pH. 5 different HSH test samples (numbered 1-5) were tested; their compositions were not identified. 50% SOR and S solutions were used as control rinses. Student's t-test for paired samples was used to compare test solutions with control solutions.	Test Substance / Minimum pH Values: Test soln / SOR / S 1: 6.39 / 6.34 / 4.11 2: 6.23 / 6.58 / 4.08 3: 6.56 / 6.51 / 4.07 4: 6.37 / 6.48 / 4.06 5: 6.42 / 6.51 / 4.06 t-tests showed the experimental solutions were statistically significantly different ($p<0.005$) from the S control minimum pH values. No significant differences between the SOR control and test substances.	Test substances were not identified. HSH solutions were slowly fermented but plaque pH did not drop below 6.0. SOR was mildly acidogenic.
Maki et al., 1983 (Ref. 48)	In vitro study to examine acid production from isomaltulose in dental plaque suspensions	12 Ss - no description	Dental plaque was collected and prepared for acid production measurement. Endogenous acid production was first measured followed by the addition of a 1% sugar soln. pH was kept constant by the addition of buffer. Acid production activity was expressed as $E \times 10^{-9}$ (E = equivalent weight) of acid per mg protein of plaque per min. Solutions used: isomaltulose, SOR, X, S.	Series 1 Mean acid (n=12) production activities: S = 20.6 (100%) isomaltulose = 9.6 (4.7%) SOR = 3.3 (1.1%) X = 0	There was little acid production from SOR and none from X in this study.

Table 1.-- Sugar Alcohols and Plaque pH, Acid Production

Study	Study Design	Subjects	Methods	Results	Comments
Park et al , 1991 (Ref 49)	In situ study to evaluate the effect of SOR and X mints on plaque acidogenicity. randomized, crossover	5 Ss, ages 25 to 46 years	Ss wore an appliance containing interproximal wire telemetry pH sensor in place of missing mandibular molars. No oral hygiene for 3 to 7 (d) while wearing prostheses. Mints - sweetened with 94% SOR (SOR) or sweetened with 79% SOR and 15% X (SOR-X) Snack foods: cookies, cupcake, granola bar (all store bought). 9X5 randomized block test design used to evaluate acidogenic potential of snacks. Resting plaque pH was taken for 5 min. Ss then ingested test snacks for 2 min. If indicated, 3 min after ingestion of snack, Ss consumed one of the mints for 5 min. Plaque pH was monitored during snack ingestion and use of the mint and then for one hr following the challenge. At end of test, Ss rinsed with tap water and reference buffer solns were applied topically to the pH probe and the stabilized electrode response was recorded. These values were used to transform readouts to pH values. Statistical analysis: Bartletts test to determine homogeneity of variances. All variances were homogenous and an ANOVA was performed.	Resting mean plaque pH: 6.97 **Lowest plaque pH attained** Test Food / No Mint / SOR / SOR-X Cookie 4.02 5.04* 5.60* Granola bar 4.16 4.68 5.32 Cupcake 4.06 5.03 5.40 *These values do not differ significantly	Authors conclude that the use of a sugarless mint reduced the acidogenicity of test snacks, when they were used 3 min following snack ingestion. SOR-X mint was significantly more effective than the SOR mint. The SOR mint was useful with only 2 of the 3 snack foods. However, final pH values did not go above 5.5 in all but one test (i.e., with the SOR/X mint). Authors suggest that the benefit from use of X or SOR-containing mints is attributed to the stimulatory effect on saliva production during snack ingestion. Saliva helps buffer oral acids.

Table 1.-- Sugar Alcohols and Plaque pH, Acid Production

Study	Study Design	Subjects	Methods	Results	Comments
Söderling et al., 1989 (Ref. 50)	Intervention to 1) investigate the effect on plaque of chewing gums that contained either X, SOR or a mixture of X/SOR and 2) compare the results with those obtained with subjects who used S gums.	28 men and women (ages 19-35 yrs, avg. age 22.5 yrs), non-smokers with a DMFS index ranging from 1 to 16, mean 8.3	4-week test period. 21 Ss (not habitual gum chewers) randomly assigned to 3 groups of 7: X (10.9 g/day), SOR (10.9 g/day) or X-SOR (8.5/2.4 g/day) in gums. 7 controls were habitual users of S gum. Test phase: 2 wks no-gum, then sugar alcohol gums for 2 wks (10 gums/day in 5 2-gum doses). Ss maintained normal diet and oral hygiene except 48 h before 2nd and 3d visits, Ss refrained from oral hygiene and kept a diet history. Plaque and saliva collected after 2 and 4 wks. S. mutans and lactobacillus determined in saliva. Resting pH of 48-hr plaque was measured and Ss rinsed mouths for 1 min with 10 mL mouth rinse containing same sugar alcohols (10% w/v) as in test gums. Plaque pH measured at 2, 5, 10, 15 and 20 min after rinse. Plaque pH repeated at above times after rinsing with a 10 mL rinse of 10% (w/v) S solution. Student t-test, Wilcoxon test, Pearson and likelihood chi-square test, Spearman test	No changes in resting pH values were noted in X and X/SOR groups whereas the use of SOR gum was associated with significantly lower pH compared to baseline values. Final plaque pH with SOR gum remained above pH 6.0. Plaque of X & X/SOR gum users showed better ability to resist pH drops induced by S rinse than plaque of SOR gum users ($p<0.05$). Baseline: habitual S gum users showed highest plaque S. mutans as compared to X ($p<0.02$), SOR ($p<0.02$) and X-SOR ($p<0.01$) groups. 2-week plaque results: decreased S. mutans in X and X-SOR groups. More than half SOR Ss showed increases. Difference between X and SOR signif. ($p<0.05$) Tendency for saliva levels of S. mutans ↑ in SOR group and ↓ in both X groups. Differences significant.	No indication of S intake in controls. Authors indicate that the results suggest that the effect of SOR on the quantity and properties of dental plaque, as well as on the salivary levels of S. mutans, varied between individuals from no effect to an unfavorable effect. The X/SOR or X gums exerted almost similar beneficial effects on plaque weight, acidogenic response to S, and occurrence of S. mutans in saliva.
Toors and Herzog, 1978 (Ref. 11)	In vitro study to determine the fermentability of a non-sugar licorice, licorice components, and regular licorice in pooled plaque/saliva mixtures; in vivo plaque pH measure.	12 volunteers - provided plaque samples	In vivo plaque pH was measured before and after licorice consumption using pH telemetry. Resting pH was determined by having the Ss chew on paraffin tablets. Ss chewed 10 pieces of licorice on day before plaque samples were harvested and pooled. Substances tested: Regular licorice (35% S); experimental licorice, the components of the experimental licorice, X, hydrogenated potato starch (HPS), and white bread suspension.	**Fermentability in plaque-saliva mixtures (as % of regular licorice fermentation)** SOR 12 Soy flour 75 potato starch deriv. 82 Exper. licorice 68 X 5 HPS 60 White bread suspen. 79 In vivo plaque pH values during consumption of: regular licorice (about 5.0), experimental licorice (about 5.5), S rinse (about 4.5).	Results of this study show that it is more than the source of sweetener that can account for the cariogenicity of a food. Some of the ingredients in the test licorice were more acidogenic than SOR. Authors note that a comparable HPS (HSH) showed critical pH drops down to pH 4.5 for powder form and pH 5.0 for syrup. Other forms of HPS have been shown to be less fermentable. Authors state that the methods used here to evaluate fermentation do not relate fermentation values to the pH of deeper layers of plaque in situ at the enamel surface. Telemetric measures showed acid production during and directly following consumption of the experimental licorice was too high to warrant labeling it as safe for teeth.

Abbreviations:

X = Xylitol
S = Sucrose
SOR = Sorbitol
LAC = Lactitol
HSH = Hydrogenated starch hydrolysates
HGS = Hydrogenated glucose syrups
MALT = Maltitol
MANN = Mannitol
ISO = Isomalt
GLU = Glucose
DMFT = Decayed, missing, filled teeth
DMFS = Decayed, missing, filled surfaces

Table 2.--Sugar Alcohols and Dental Caries--Continued

Study	Study Design	Subjects	Methods	Results	Comments
Bánóczy et al., 1981 (Ref. 21)	Intervention, double blind study to determine influence of SOR-containing sweets on caries increment	535 children, ages 3-12 years, living in a children's home in Hungary	3-year study: 405 were evaluated at end 1st year; 326 at the end of second year; and 258 (131 in test group; 127 in C group) at end of 3d year. Loss of children over the 3 years was due to adoption of the children and other undefined causes. Test group consumed 8 g/d SOR-containing sweets between meals; control group - 8 g/d S-containing sweets . Ss examined 6 times - every 6 months at beginning. Caries increment determined by DMF means of teeth and teeth surfaces, periodontal and oral hygiene conditions also assessed.	No signif. differences in groups at baseline. **Mean DMFT Values:** Exam / SOR Group / S Group 1 / 1.25 / 1.36 2 / 1.84 / 1.80 3 / 2.39 / 2.69 4 / 2.84 / 4.42 5 / 3.72 / 6.29 6 / 4.93 / 7.40 **Caries Increment - comparing SOR to S** SOR / S First year: 1.02 / 2.61 p<0.001 Second yr: 0.90 / 1.86 p<0.001 Third year: 1.18 / 1.13 NS	Authors note that the reduction in caries increment for the SOR group in the 3rd year may be related to the fact that the children in the SOR group traded sweets with the S group. The differences in the 3rd year values were neither clinically nor statistically signif. Authors also explain that the lack of signif. in the 3rd year may be caused by adaptation of micro-organisms to SOR, in addition to other factors. The control group received S-containing sweets between meals, whereas the test group received SOR sweets. The SOR group still developed dental caries, but signif. less than the S group. This does not support "non-promotion" caries claim with SOR; only "less than S." This protocol should have been approved by an Institutional Review Board due to the deliberate development of dental decay, which is viewed as unethical. Authors note that they were not completely successful in maintaining the double blind character of the study from the 2nd year on. This was due to the special taste attributes of SOR compared to S. Statistical methods not given.
Bánóczy et al., 1985 (Ref. 27)	Intervention study (WHO X field study in Hungry) II. General background and control of dietary regimen	286 institutionalized boys and girls, ages 8-13 years; Ss, from 8 institutions, were divided into 3 groups: fluoride, X, and control.	X intake: not to exceed 20 g X/day, average intake between 14 and 20 g/day. 3 pieces chewing gum/day (after bft, lunch, dinner), with supplemental sweets available within acceptable dose range between meals. X-containing (10%) sodium monofluorophosphate (0.8%) dentifrice used 2 times/day. Diet questionnaire, based on 24 hr recall, used to evaluate S- and X-containing products. X intake limited to solids; S both solid and liquid. Frequency of consumption calculated separately for weekday and weekends. Fluoride intake was evaluated via periodic surveys of fluoride level in drinking water, milk, dentifrices and urine. Statistical Analyses: Student's paired and unpaired t-tests	S intake: 1. In liquid form lowest between meals at all institutions. 2. Increased intake on weekends at all institutions, except 1. 3. Increased total intake in all groups on weekends (p< 0.001). X intake: 1. Lower intake on weekends (p< 0.001). 2. Substitution for S lower on weekends. Fluoride intake: 1. Concentration in drinking water was extremely variable (0.2 - 4.2 ppm); urinary F/creatinine quotient reflected this trend.	Living and dietary conditions varied considerably between weekday and weekend. Majority of X products were consumed at meals. 3 mos prior to end of study, milk fluoridation program at 1 institution (Fot) was discontinued due to kitchen remodeling. Subjects in this group were in the fluoride group. Authors concluded that consumption of X-containing products did not reduce frequency of intake of S. If this were true in the general population, and adding X to a S diet reduced caries incidence, then it would lend support to X as a caries reducing agent. However, one cannot infer that from this study.

Table 2.--Sugar Alcohols and Dental Caries--Continued

Study	Study Design	Subjects	Methods	Results	Comments
Barmes et al.. 1985 (Ref. 29)	Intervention to compare the efficacy of three fluoridated products in order to select the product most suitable for local conditions (WHO field trial - Thailand and French Polynesia)	In both locations approximately 750 children, 250 each of ages 6-7, 9-10 and 12-13 years (non-test)	Approximately 3-year field trial in Thailand (3 groups) and French Polynesia (4 groups). In most groups, n = approx. 250 or more. Products tested both locations: Group 1: fluoride rinse, group 2: S-fluoride gum, and group 3: X (51%)-SOR-fluoride gum. Group 1 rinsed with fluoride rinse 1 min. every 15 days, Grps 2 and 3 chewed 4 sticks gum/day. Groups 1 and 2 began study in Oct. 1977; group 3 began study July, 1978. In Dec. 1978, a fourth group began in Polynesia only; this group used a non-fluoridated gum with X (51%)-Sor sweeteners. The 12-13 year old Ss were given dental exams to be used as a comparison with 9-10 yr old Ss who would be 12-13 yrs at end of study. Approx. 250 6-7 yr. olds examined at end of studies to determine caries prevalence trend in community irrespective of preventive agents. Baseline and final exam of DMFT and final DMFS. A random sample of approx. 100 from each age and region examined at 18 months	Thailand: For each group, 7 yr old test Ss at baseline had considerably more dental caries than 7 yr old Ss examined at end of study. Thailand: Group 1 2 3 Age at baseline vs final results 7 10 7 10 7 10 DMFT 1.26 1.63 0.96 2.01 0.61 1.14 DMFS 1.66 2.73 1.43 3.91 0.78 1.72 1 2 3 10 12 10 12 10 13 DMFT 2.28 2.80 1.71 2.63 1.59 2.33 DMFS 3.93 5.21 3.12 5.20 2.73 4.57 Polynesia Group 2 3 4 Age at baseline vs final results 7 10 7 10 7 10 DMFT 0.97 4.16 0.74 2.95 0.81 3.99 DMFS 1.21 5.19 1.07 3.42 0.97 4.94 2 3 4 10 13 10 13 10 13 DMFT 3.69 9.55 2.48 6.80 3.02 8.08 DMFS 5.79 11.99 4.22 8.50 4.04 10.76	Gum contained X, SOR, and fluoride which confounds the results for X or SOR by themselves. Amount of S, X, and SOR in the gums was not reported. Large number of Ss dropped out of study due to change in schooling system, transport problems etc. In Thailand delay in supply and use of fluoridated X-SOR gum and logistic problems. Doubts raised about compliance in both regions. Authors try to account for the multiple confounding factors associated with field studies. No indication of randomization of subjects. Total dietary intake not indicated. In Polynesia, DMFT and DMFS scores indicated that fluoridated X-SOR gum was the only regime which has come close to controlling the caries process. As expected, the trend is that the group chewing SOR-X-fluoride gum has a lower caries rate than the group chewing S-fluoride gum, and both gum groups do better than just the group receiving a fluoride rinse.

Table 2.--Sugar Alcohols and Dental Caries--Continued

Study	Study Design	Subjects	Methods	Results	Comments
Frostell et al., 1974 (Ref. 31)	Intervention to determine the effect on caries increment of substitution of HSH for S in candy (The Roslagen Study)	225 children,: ages 2-1/2 to 4 years	1-1/2 to 2-1/2 year study. Test group consumed candy with HSH. Composition of carbohydrate component of candy: SOR 10%, dimeric saccharide alcohols (mainly mannitol) 7.5%, trimeric saccharide alcohols 7%, tetrameric saccharide alcohols 7%, pentameric saccharide alcohols 6%, hexameric and higher saccharide alcohols 62%. No HSH gum was made but Ss in test group allowed to chew SOR gum. Candy consumption checked by use of a coupon system. Parents bought candy and storekeepers returned coupon to investigators. C group consumed S candy, also bought with coupons. Not all parents and storekeepers followed through on use of coupons. Ss examined clinically twice a year for total of 6 times (K1-K6). DMFS and DMFT index calculated at each exam. Plaque quantity and any gingival inflammation were also recorded. Periods K1 and K2 - baseline (no intervention). Statistical methods not reported.	Out of 225 Ss, 113 participated through the entire experimental period. Reasons for dropout are given in the study. At baseline and during observation period, K1-K2, there was no statistical difference between HSH and control groups in DMFS. **Caries increment, periods K2-K4 (baseline to 1 yr intervention)** C DMFS: 1.10; HSH DMFS: 2.79; C DMFT: 1.84; HSH DMFT: 1.67 Per cent difference: 15.5 (DMFS); 9.2 (DMFT) **Caries increment, periods K2-K5 (baseline to 1-1/2 yr intervention)** C DMFS: 4.70; HSH DMFS: 2.86; C DMFT: 2.76; HSH DMFT: 2.10 Per cent difference: 27.0 (DMFS); 23.4 (DMFT) **Caries increment, periods K2-K6 (baseline to 2 yr intervention)** C DMFS: 6.95; HSH DMFS: 5.97; C DMFT: 1.67; HSH DMFT: 2.79 Per cent difference: 14.1 (DMFS); 24.0 (DMFT) None of the differences between groups was statistically significant.	Authors state that an analysis of coupons (given to the HSH group) sent in by store owners showed a smaller number than coupons from the control group. Inquiry with parents of children in HSH group revealed that they gave their children other candy as well and that HSH candy varied from 50 to 75 percent of total candy consumption. Authors reported that some investigators over recorded and others under recorded dental caries. Since exams were every 6 months, authors state that it was possible to correct most of the effects of the differences in diagnosis. Authors state the results show a tendency for reduced caries with HSH; this tendency was most obvious after 1-1/2 years of intervention but decreased after 2 years, which is unexpected. Due to the problems in this study of poor compliance, inter-examiner variability, lack of blinding, and inconsistent results, the results of this study do not support significant dental benefits from use of HSH candies in place of S-containing candies.
Glass, 1983 (Ref. 32)	Intervention to evaluate the cariogenicity by regular use of SOR gum, randomized	540 children, ages 7-11 years in a nonfluoridated area	2 year study. Ss randomly assigned to one of two groups; although all Ss living at the same street address were assigned to the same study group. Control - no gum group; Gum group (2 sticks per day). 4 sticks available for use at home. Intake of SOR from gum not reported. Examinations yearly. Examiners were blinded as to the group assignment of each child.	43 dropouts from the study due to changes of school or residence. There were no significant differences between groups in age, sound teeth, surfaces at risk of caries, and past caries experience. There were no statistically significant differences between groups over the two year period. **Analysis of mean caries increments over 2 years** New DF teeth: SOR 2.53; Control 2.55; t 0.09 New DF surfaces: SOR 4.63; Control 4.70; t 0.15 n: SOR 269; Control 271	Authors state that the amount of gum chewed by the Ss in this study was around 3-8 times greater than the estimated 90th percentile. Composition of gum was not given. Mean SOR intake was not given. Mean daily S intake of the groups was not given. Gum chewing has been demonstrated to have an anti-caries effect, regardless of sweetener, by stimulating saliva which buffers pH and provides calcium and phosphorus to aid remineralization of enamel. Because this effect was not considered in this study, it is inconclusive to state the effect, if any, that SOR contributed to the lower caries rate in the test group.

Table 2.--Sugar Alcohols and Dental Caries--Continued

Study	Study Design	Subjects	Methods	Results	Comments
Creanor et al., 1992 (Ref. 37)	Clinical study to evaluate the effect of chewing gum for 20 minutes on in situ enamel lesion remineralization compared to a fluoridated dentifrice; crossover	12 adult Ss	2 7-week crossover tests: 1. SOR gum (n=6), no gum C (n=6) and 2. S gum (n=6) and no gum C (n=6). 10 Ss were common to both studies. Lower appliances were constructed for each Ss. All Ss used fluoride dentifrice 4 weeks before study and during each test period. Ss brushed twice daily for 2 min with a pea-size amount of toothpaste. Appliances were worn at all times. A 1 week's diet for each Ss was recorded. A copy of the diet was given each person with the request that each keep a similar diet in test and C phases. Snack foods given twice a day between meals. Test Ss chewed 5 sticks gum/d for 20 min: one after each meal and snack. Test gum: SOR + some HGS and aspartame; S gum with S and GLU. Artificial enamel lesions were created *in vitro* in human premolars and coated with acid resistant nail polish. Teeth were immersed for 5 days in a demineralization soln (pH 4.5). Baseline mineral content measured. Microradiographs were taken of enamel sections and mineral content made. Difference between baseline and final value calculated for mineral loss (ML), surface zone (SZ), and lesion body (LB) mineral content. Baseline value and mean of all lesions used for determination predicted changes for all Ss in test and C phases. A weighted ANOVA was used to predict changes.	**SOR Gum**: The total mineral loss after 7 weeks corresponded to a remineralization value of 18.2% ($p<0.001$) compared to the baseline average. The control value was 12.1% remineralization compared to baseline ($p<0.01$). No significant differences between test and C for remineralization values or for SZ and LB values. **S gum**: Total mineral loss after 7 weeks corresponded to a remineralization value of 18.3% ($p<0.001$) vs. baseline average. The control value was 10.8% remineralization vs. baseline ($p<0.01$). No significant differences between test and control for remineralization values or SZ values. For remineralization of the LB, the S gum value was significantly higher ($p<0.01$) than the C.	Results of this study show that chewing gum per se is beneficial to teeth regardless of the sweetener used. Authors report a significant difference in remineralizaton in favor of the S gum when considering the mineral content of the lesion body. Authors state that chewing gum for 20 min. after meals or snacks should minimize deleterious effects of the S gum. Authors note that other studies have shown no signif. difference in the ability to stimulate salivary flow rate and to raise plaque pH after 20 min. of chewing S gum vs. a sugar-free gum. Chewing S gum for less than 20 min. did not neutralize as much acid. Authors conclude that the increased salivary flow that occurred during gum chewing in this study helped to accelerate the rise in plaque pH, reduce the tendency for demineralization, and to enhance lesion remineralization beyond that for dentifrice alone.

Table 2.--Sugar Alcohols and Dental Caries--Continued

Study	Study Design	Subjects	Methods	Results	Comments
Ikeda et al., 1975 (Ref. 33)	Clinical study to evaluate the cariogenicity of maltitol and a polysaccharide alcohol (HSH) using human intraoral test and cariogenicity test in rats	Number of subjects not specified	Intraoral Cariogenicity Test (ICT) was used: Cow enamel fragments were adhered to resin-made gum of the submaxillary denture at the position of right and left molars. The denture was used by the subject in a normal way. Enamel fragments were extraorally dipped in 3% MALT or HSH solutions for 1 min/day. The control fragment was dipped in 3% S daily. Hardness was measured 1 week later. Sprague-Dawley SPF rats, 4 weeks old, were inoculated with S. mutans and divided into 2 groups. One group was given feed with 26% sugar alcohol and 10% starch mixed for 75 days. Another group was given Keyes-2,000 feed without S.	Decalcification in MALT group was 1.66 (n=16). HSH showed higher decalcification compared to MALT but they were significantly lower than S (values not reported). Decalcification in S group (n=16) was 2.70 (significantly different from maltitol group). Results of rat study show the caries score for the S group (n=5) to be 45.8; for the MALT group (n=5) the score was 3.2. MALT was significantly less cariogenic than S.	Details of study and number and description of subjects were not given. No indication that diets were controlled. Bovine enamel was used. A control group should have been provided in which the bovine teeth were soaked in pure water, rather than assuming the decalcification would be 0 if no sugar were used. Authors state that it is complicated to evaluate the results under this experimental method. Indigenous cariogenicity in ICT varies according to each individual and is influenced by saccharide intake of daily diet. Under these experimental conditions, author states that decalcification of enamel by MALT as intraoral substrate is close to zero. Results of this study are difficult to interpret.
Kandelman et al., 1988 (Ref. 30)	Intervention to study effect of partial substitution of S by X on development of caries (WHO X field study in French Polynesia)	746 children, ages 6-12 yrs	32-month study with 3 groups. C group - 345 Ss of Bora Bora supplied with toothbrushes, fluoridated dentifrice and regular instructions in oral hygiene; X1 group - 240 Ss of Rangiroa; X2 group - 161 Ss of Maupiti. Daily portion of 20 g X given with various products e.g (chewing gum, hard candy, chocolate, wafer gumdrop and ice lolly). Complete oral exams given at baseline, and after 8, 20 and 32 months. Interproximal surfaces of incisors routinely inspected. Standardized bite-wing radiographs taken at each exam from Ss older than 8 yrs. Plaque index determined in 9 and 10 yr subjects. ANOVA used to assess the baseline caries data. Caries increment (CI) and CI rate assessed for between group and between treatment differences using ANCOVA with baseline data as covariate.	468 subjects completed study. 278 subjects were dropouts. Intra-and inter-examiner reliability indicated high level of agreement in caries scoring. Poor oral hygiene noted in all treatment groups. Treatment group / n / Caries increment / Caries increment rate X1 / 164 / 4.58[a] / 4.95[a] X2 / 109 / 4.37[a] / 5.11[a] C / 195 / 7.19[b] / 9.09[b] Statistical evaluation: mean values of groups with different superscripts are signif. different. Signif. reduction of caries increment rate by 37 and 39% in 2 X groups vs the C group. For all but one age class (6 yr olds), the highest caries increment rates occurred in C group. Poor oral hygiene observed in all treatment groups. No differences between 2 X groups. Larger differences between C vs X groups found in older subjects.	37.3% of the Ss dropped out. Most children were leaving school at age 13. X2 group had no subjects with initial age of 11 and 12 yrs. Not clear as to whether all subjects on study were already receiving fluoridated toothpaste and regular instructions in oral hygiene. No gum without sweetener used. Caries increments and caries increment rates were pooled for all age classes for each treatment. Ss were not randomized to groups nor the test double-blinded. Ss compliance with study protocol not indicated. Total dietary intake not indicated. Authors noted that the cariostatic potential of X was confirmed under realistic conditions. The authors also state that "the mere substitution of sugar in certain foods and the resulting decreased frequency and time of sugar exposure have undoubtedly contributed to the observed effect." Therefore, the question remains whether X is truly cariostatic or less cariogenic than sugar.

Table 2.--Sugar Alcohols and Dental Caries--Continued

Study	Study Design	Subjects	Methods	Results	Comments
Kandelman and Gagnon, 1987 (Ref. 22)	Intervention study to evaluate the effects of chewing gum containing X on incidence and progression of caries.	433 children of low socioeconomic status with high caries rate, ages 8 and 9.	One year study. 13 elementary schools involved, all same experimental group/school. 2 experimental groups received chewing gum 3 times/day; chewing time was 5 min. A third group received no gum. 1 group (X65) = 65% X (1.1 g/stick) gum; total daily X intake = 3.4 g. 2nd group (X15) = gum with 15% X (0.3 g/stick) + 50% SOR (0.8 g/stick); total daily X intake = 0.8 g. Preventive program consisted of 3 sessions of oral hygiene instruction with periodic brushing control, weekly 0.2% sodium fluoride (NaF) mouthrinse. Dental examination criteria was that used in previous clinical trials and scores based on WHO standards. Plaque distribution assessed by a modified Plaque Index (PI). Net progression of decay obtained by subtracting number of reversals from number of progressions of decay. Each subject analyzed by same examiner throughout study. Calibration between examiners carried out prior to study. Statistical Analyses: ANCOVA for net progression of decay and DMFS increment; chi-square test to analyze medical questionnaire.	**Net progression of decay (NPD)** was signif. lower in the X65 group (1.25) than in X15 group (1.87) ($p<0.05$). Each X groups had signif. ($p<0.001$) less NPD than control. **Adjusted mean NPD**: control: 3.53 surfaces; X groups: 1.59* ($p<0.001$) **DMFS increment** was lower in Ss that chewed gum (1.58) than those that did not chew (1.28) ($p<0.001$); No significant differences in X groups (high = 1.34, low = 1.78). Buccolingual surface progression of decay was 0.82 for X15 Ss and 0.41 for X65 Ss ($p<0.05$); both of the X groups fared better than controls (1.7; $p<0.001$). Occlusal and Approximal surfaces progression of decay did not differ between X groups, but was signif. higher in controls than in X groups ($p<0.001$).	Because there was no signif. difference between the DMFS increment of the 2 X groups, the only conclusion from this trial is that the DMFS was lower in gum chewers than non-chewers, regardless of sweetener. Data adjusted for age and sex, but no mention if any differences were found. No information given as to diets children were consuming other than they maintained dietary habits with high S intake. No dietary records kept. Gum may have displaced S-containing sweets. Authors do not state if the control groups had access to any gum during study and if so what type. Ingredients other than X and SOR in gum not mentioned. Authors noted a signif. examiner effect as indicated by the analysis of covariance, but the differences in the assessment of caries progression were independent of the study group.
Leach et al., 1989 (Ref. 35)	In situ study to determine the effect on the potential for remineralization of artificial caries-like lesions in human enamel with SOR	10 adults	Artificial white spot lesions were prepared in enamel surfaces of human teeth and set into intraoral cast silver bands. One band was attached to a lower first molar tooth. Bands were worn for 2 3-week periods during which Ss continue to use normal oral hygiene procedures (including fluoride dentifrice). Drinking water contained no fluoride. No diet instructions were given. Ss given snack foods (candy, raisins, chocolate wafer, creamed-filled cupcake) and instructed to consume one each morning and afternoon between meals. Snacks were selected randomly. During one of 2 experimental periods, Ss chewed 5 sticks gum per day, each for 20 min., immediately after breakfast, lunch, dinner, and snacks. The gum contained SOR with small amounts of MANN, HGS, and aspartame. During second experimental, Ss consumed snacks but no gum.	**Microradiographic assessment of mineral content of lesions before and after intra-oral exposure** O = original lesion N = no gum period G = SOR Gum period mean values (n=10) O / N / G **Integrated mineral loss, delta Z, vol% x µm** 1422 / 1183 / 1010 **Minimum mineral content (vol%)** 56.3 / 62.7 / 69.0 **Depth of lesion, µm** 104.7 / 99.1 / 94.6 Analysis of variance: variance due to treatment, $p<0.0001$. Differences between treatment means: $p<0.01$, all parameters	It would be helpful to compare these results to those with a S gum, particularly when gum is chewed for 20 minutes. Significant remineralization of original lesions occurred during the absence of chewing gum. Authors state the use of gauze to promote plaque retention with intraoral devices could in the presence of a cariogenic diet promote demineralization or remineralization (because of a concentration of calcium and phosphates in plaque and fluoride from dentifrice). Authors state that it is unknown to what extent remineralization was dependent upon duration and timing of gum-chewing. They state that the effect of gum is likely to be maximized by administration immediately after a cariogenic meal or snack, so that it can be chewed long enough to reverse the pH fall of plaque.

Table 2.--Sugar Alcohols and Dental Caries--Continued

Study	Study Design	Subjects	Methods	Results	Comments
Moller and Poulsen, 1973 (Ref. 20)	Intervention to determine the effect of long term chewing of SOR gum on incidence of dental caries	Group 1: 174 children, 8-12 years old (School T) Group 2: 166 children, 8-12 years old (School K)	2 year study. SOR-containing gum: 1.2 g SOR and 45 mg calcium phosphate Group 1 chewed 3 tablets SOR gum daily: one in morning, one after lunch, one after dinner Group 2: control (C) no gum Dental caries recorded by the following criteria: 1= initial dental caries without loss of substance; 2= loss of substance in enamel; 3= dentinal caries; 4= pulp involvement	Mean number of erupted teeth increased from about 18 per child at start of study to about 24 per child Ss from Group 2 had marginally more teeth erupted than Group 1. Number of missing teeth were nearly identical between groups. At start of study sound tooth surfaces were signif. less frequent in Group 1 (4%) than in Group 2 (2.2%). During 2-yr study, frequency of sound tooth surfaces ↓ in Group 1 (81.9% to 82.6%); Group 2 reported a reduction (84.7% to 83.9%). The frequency of filled tooth surfaces in the 2 groups also suggested a smaller caries increment in Group 1 than in Group 2. The relationship between untreated dental caries and fillings showed that Group 1 had a smaller caries increment, differences were significant.	28 Subjects (Ss) failed to finish study. Gum contained calcium phosphate which acts as a buffer in saliva to help maintain pH and aid remineralization. More importantly, the control group chewed no gum at all, so this lack of salivary stimulation is a large confounder Also, the study was not blinded. Authors note that differences could be related to chewing gum, reduced consumption of S-containing sweets, increased salivation, differences as to the time of dental treatment, intra-examiner variability in maintaining the diagnostic criteria and differences in the "natural" caries progression pattern between the two groups.
Rekola, 1986 (Ref. 23)	Assessment of results from 2-year Turku sugar study with regards to the progression of incipient carious lesions on buccal smooth surfaces; comparison of S with X.	33 Ss S group; 47 Ss X group	See Turku methods - almost complete substitution of X for S in diet (Ref. 24). Color dental pictures taken of Ss in S and X groups during the original Turku 2-year sugar study were examined. Photos, taken after 2 months and at 24 months, were of right and left sides and of the front of maxillary and mandibular teeth. White lesions of teeth 16-26 and 36-46 were measured. Total of 35 white spot lesions in 11 Ss in S group and 60 white-spot lesions in 16 Ss in X group were measured. Teeth of all Ss also examined with stereo-microscope (teeth 15-25 and 45 to 35). Statistics: absolute method error, paired t-test, Wilcoxon test, Student's t-test, Mann-Whitney U-test	S group showed tendency for increasing size in white spot lesions (NS) and a decrease of lesion area in X group ($p<0.01$). At 24 months, the mean area of white-spot lesions in X group was signif. smaller ($p<0.01$) than in S group. In S group area of white-spot lesions increased in absolute values ($p<0.05$). Results of stereo-microscope exam gave similar result: originally quantified caries scores (CIS) increased in S group and decreased in X group. Differences were signif. ($p<0.001$)	Authors note that results indicate that X consumption caused remineralization of incipient white-spot lesions on buccal surfaces. Comparison is of X-consuming group to S-consuming group. The results do not support a non-promotion claim of X without a comparison; to do so in this study, there would need to be another group which received neither S nor X.
Rekola, 1987 (Ref. 25)	Assessment of results form 2-year Turku sugar study with regards to quantifying changes in size of approximal carious lesions with dietary substitution of X for S	Same as Ref. 23	Same as Ref. 23 Condition of distal surfaces of the canines and that of the mesial and distal surfaces of premolars and first and second molars were recorded from radiographs. Total surfaces examined were 1,188 in S group and 1,692 in X group. Ss did not receive fluoride treatment during trial. Criterion "carious" was used when there was a radiolucent area involving part of the enamel, or up to the amelodentinal junction. Advanced lesions were filled during the study. Criteria "overlap" or "unreadable" were used when contact surfaces of neighboring teeth were overlapping or when the surface was not shown on film. Projections of approximal lesions on bite-wing radiographs were analyzed planimetrically. Statistics: same as Ref. 23	Results showed highly significant ↓ in approximal lesion size in S group; X group lesions remained unchanged. Corresponding difference in size of lesions between X and S groups after 2-year study was highly signif. ($p<0.001$)	Authors concluded that ad libitum consumption of S enhances further progression of carious lesion, whereas X consumption favors arrest and decrease of the lesions. Without a group consuming neither S nor X, it is difficult to attribute enamel remineralization and arrested caries development to X consumption, rather than to the absence of S.

Table 2.--Sugar Alcohols and Dental Caries--Continued

Study	Study Design	Subjects	Methods	Results	Comments
Rundegren et al., 1980 (Ref. 36)	In situ study to evaluate S substitutes for their contribution to demineralization of bovine enamel slabs	Group 1: 4 male students (age 19) Group 2: 4 Ss (ages 56 to 59 years with dentures)	Intraoral devices with bovine enamel mounted on acrylic blocks were used with Group 1. Partial dentures with enamel slabs were used in Group 2. All devices were placed in the buccal region of the first molars. Sweeteners: 10% (w/v) of S, MALT, HSH. Each was tested for 4 weeks. S was used as a positive control for demineralization. A 0.9% sodium chloride (NaCl) soln was a negative control during 2-week test. Ss immersed experimental sites of their appliances 4 times daily, 10 min each, in cups containing soln. After immersion, appliances were returned to the mouth. At end test week, plaque was collected and plated. Samples were examined for S. mutans. Degree of demineralization was also measured before and after each test week.	A comparison of enamel hardness with 10% HSH vs NaCl showed slightly higher values for demineralization with NaCl. Results with HSH vs S and MALT vs S showed greater demineralization of enamel with S. The differences were significant at 1% level (Student's t test). Demineralization in MALT and HSH groups was associated with dietary effects. S showed an effect on demineralization above that of the diet.	Small number of subjects; the mean of the results was not given. Authors state that HSH, in comparison to NaCl, did not contribute to enamel softening and measured changes in microhardness reflects background intake of fermentation of dietary carbohydrates. Authors state that elderly Ss showed a higher degree of demineralization than the adolescents.

Table 2.--Sugar Alcohols and Dental Caries--Continued

Study	Study Design	Subjects	Methods	Results	Comments
Scheinin et al., 1985 (Ref. 26)	Intervention trial (WHO X field studies in Hungary) to examine the effects of partial replacement of S in sweets and confectionery with X on incidence of caries.	689 institutionalized children (410 boys, 229 girls), ages 6 - 11. Ss were from 11 institutions in Budapest, Hungary.	3-yr study. X group, n = 278: max intake 20 g/day X in chewing gum, chocolate, gum drops, tictacs, and wafers. X group also used fluoride dentifrice. Fluoride group, n = 266: no X, but received fluoride in dentifrice, milk and water. C, n = 145: received no fluoride or X. (See Ref. 49 for details of intakes of groups) Oral registrations made initially and yearly by 2 teams. Inter- and intra-examiner errors were accounted for throughout study; Proportion of agreements between examiners was 94% -96% which included quantitative and qualitative development of caries and 96% - 98% for quantitative development only. Caries registrations made without knowledge of results from previous examiner. Caries increment rate (RT) determined from changes in DMFT for teeth at risk. Molar and premolar teeth divided into 5 surfaces- occlusal, mesial, buccal, distal and lingual. Transillumination of teeth was done with fiber optics system. No radiographic assessment. Caries codes: 1 = initial caries, no loss enamel; 2 = enamel caries; 3 = dentin caries; 4 = caries with pulpal involvement. Statistical Analyses: Kruskal-Wallis test for overall comparison of differences; Mann-Whitney U-test for differences between groups; ANCOVA for 3 yr caries increments and rates over base-line prevalence. Note: In a large number of instances the SD is equal to or larger than the mean.	Significant differences between groups in age, sex, number of sound surfaces, number of decayed surfaces and number of filled surfaces at base-line. X group had signif. higher caries prevalence. At 3 yr, X group had lower caries increment, $D_{1-4}MFT$, ($p<0.001$) and increment rate of decayed teeth, RT_{1-4}, ($p<0.002$) than fluoride or controls; there were no differences between fluoride or C; no differences between any of the groups in $D_{1-4}MFT$ and increment rate RT_{1-4}. Stable caries increment in X group for all ages; increasing incidence of caries in fluoride and C groups, especially in 10 yr olds. Considerable variation between institutions at baseline and 3 yr. At 3 yr, X group had lower incidence and caries increment rate ($D_{1-4}MFS$ and $D_{1-4}MFS$) than fluoride or C groups ($p<0.001$); fluoride group had lower incidence and rate ($D_{1-4}MFS$) than C ($p<0.01$). Caries rate highest for occlusal surfaces in all age groups, espec. 7 yr olds; buccal and lingual surfaces in X group had consistently lower incidence and rate than other 2 groups. In 7, 8 and 9 yr olds, no difference between X and fluoride groups in $D_{1-4}MFT$ in anterior teeth; incidence was lower in posterior teeth in X group than other groups. Caries scores of anterior teeth lower in fluoride than C and X groups in 7, 8 and 9 yr olds; 10 yr olds X group lowest scores.	301 subjects dropped-out; Ss in X group were older and those in fluoride were younger than those that remained in study. Caries scores in the dropouts were lower at baseline than those remaining in study. Authors noted that when comparing dropouts to the remaining subjects, there was no bias favoring treatment effect with regard to age and caries prevalence. X products were traded, especially during last yr of study, between institutions with subjects not in X group. Institutions previously assigned to fluoride group were transferred during 1st yr to control and visa versa due to extreme fluctuations in fluoride drinking water levels. Authors noted that substantial part of examiner error was due to differential diagnosis of fissure caries between intact and degree 1 lesions and evaluation of surfaces at border of 2 adjacent surfaces. Authors note that results from this study were obtained under conditions where caries prevalence and incidence are still high. Control group consisted of children with less caries than other 2 groups at base-line examination and this was attributed to diet.

Table 2.--Sugar Alcohols and Dental Caries--Continued

Study	Study Design	Subjects	Methods	Results	Comments
Scheinin et al. 1985 (Ref. 23)	Substudy of intervention study (WHO X field studies in Hungary) to evaluate effects of partial replacement of S with X on 2 yr caries increment.	976 institutionalized children, ages 6 - 12.	See Ref. 27 for details of dietary methods. This study differed from 3 yr one in that baseline differences were eliminated because new subjects entering study during the 1st year were included in this study. 2-yr caries increment was analyzed separately for each age. Codes, categories, and criteria for caries and other oral registrations were based on standard methods described in Ref. 26. Statistical Analysis: ANCOVA; Kruskal-Wallis test	DMFS increment at 2 yr was 3.8 in X group, 4.8 in fluoride groups and 6.0 in C group. RS (ratio between caries incidence and tooth surface population at risk) was 4.5 in X group, 5.5 in fluoride and 7.5 in C group. X group had a 37% and 21% lower caries increment and 40% and 18% lower incidence rate than C and fluoride groups, respectively ($p<0.001$). The differences in DMFS was significant between the X and C groups at each age ($p<0.05$-0.001); between X and fluoride group, differences only significant at age 11 ($p<0.002$); between fluoride and C groups difference only significant at age 9.	Authors noted that 42% of Ss from main study were in substudy. Total number of drop-outs was 243 (20%). (primarily due to adoption and to a lesser extent transfer to other institutions). Subjects analyzed at baseline and final examination were the same, but the intermediate examination had a number of absentees, especially in X group. The majority (67%) of the Ss used X for a full yr prior to establishing baselines. New Ss in the X group had partial substitution for S with X 6 mos before start of this study. A substantial number (exact number or % not given) of new 6 and 7 yr olds in fluoride group were exposed to milk fluoridation for a 3 yr period prior to baseline. Authors stated that the low caries incidence in these age groups could be due to this. This study provides further support that X, when substituted for S, results in lower caries incidence.
Yagi, 1989 (Ref. 34)	In situ study to evaluate the change in enamel hardness from maltitol	3 female and one male Ss, ages 42-54 years with deficiencies in submaxillary molars and wearing lingual bar denture	Intraoral cariogenicity test using bovine enamel held in a denture. While wearing the denture, about 0.08 mL of 3% MALT soln was dropped on one of 2 enamel fragments. On other fragment, 0.08 mL of 3% S soln was dropped. Ss had no dietary restrictions. After 7 days, enamel hardness was measured. Hardness is shown as depth in µm of depth that the diamond head of micro hardness scale penetrated. The experiment was repeated on each Ss.	The average change in hardness compared to pretreatment levels was 1.47 µm for MALT and 3.35 µm for S. These changes were significant as well as the difference between MALT and S treatments.	Bovine enamel was used. The bovine enamel should also have been exposed to pure water. Authors note that there were considerable differences in responses when examining individual responses to S and MALT. Differences are attributed to differences to the oral environment (e.g., plaque bacteria and quality and quantity of saliva).

Abbreviations:

X = Xylitol
S = Sucrose
SOR = Sorbitol
LAC = Lactitol
HSH = Hydrogenated starch hydrolysates
HGS = Hydrogenated glucose syrups
MALT = Maltitol
MANN = Mannitol
ISO = Isomalt
GLU = Glucose
DMFT = Decayed, missing, filled teeth
DMFS = Decayed, missing, filled surfaces

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