# History, Safety, and Dental Properties of Xylitol


## By

## Professor Kauko K. Mäkinen

*Institute of Dentistry, University of Turku, Finland*


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## 1. Introduction

Xylitol is a five-carbon sugar alcohol, a natural carbohydrate which occurs freely in certain plant parts (for example, in fruits, and also in products made of them) and in the metabolism of humans (1). Xylitol has been known to organic chemistry at least from the 1890's. German and French researchers were obviously the first ones who made xylitol chemically more than 100 years ago. This reaction was accomplished by means of sodium amalgam reduction of D-xylose (wood sugar). Owing to the obvious impurity of the then raw material, the first xylitol preparation was a syrupy mixture also containing small amounts of sugar alcohols other than xylitol. The definitive characterization and purification of xylitol to polarographic purity was accomplished already in the 1930's. The first successful crystallization of xylitol, after reduction of purified D-xylose, took place during the Second World War. This product was not, however, a stable form of xylitol. A stable, crystalline form was obtained slightly thereafter.

Although xylitol has a relatively long organic chemical history, the first half of this century was rather eventless from xylitol's point of view; xylitol was regarded as one of the numerous sweet carbohydrates organic chemists isolated at those times. Scientists obviously did not realize the biologic properties of xylitol until researchers started to exploit its insulin-independent nature after the World War II. Frontrunners in these developments were Japan, Germany and the [former] Soviet Union. In Japan, xylitol was used, for instance, in the resuscitation of patients from diabetic coma.

Xylitol thus remained mostly as a research chemical until the war-associated sugar shortage in some countries, such as Finland, forced engineers and chemists to search for alternative sweeteners. Such substances were supposed to be present, for example, in hardwood. Researchers and engineers at the former Finnish Sugar Co. Ltd. succeeded to develop an industrial procedure for small-scale xylitol production, but the matter was temporarily put aside in the advent of peace; the sugar shortage subsided. The idea was not totally forgotten, however, and the process was being gradually improved. In 1975 the Finnish company began the first truly large-scale production of xylitol in Kotka, a small town located in South Finland. Simultaneously, a Swiss company (F. Hoffman La-Roche) had shown interest in xylitol. The two companies founded a joint venture

(Xyrofin) in 1976. Later, Xyrofin became a wholly-owned subsidiary of the Finnish Sugar Co. (currently Cultor). At the same time, other companies located in the [former] Soviet Union, China, Japan, Germany, Italy, etc. had produced xylitol mostly for domestic markets. Before 1970, xylitol was mainly used in these countries as a sweetener in the diabetic diet or in parenteral nutrition (infusion therapy). Use of xylitol for dental purposes commenced in the 1970's: the first xylitol chewing gum was launched in Finland in 1975 and in the USA in the same year but a few months later.

Various forest and agricultural materials rich in hemicellulose have been used as a raw material in xylitol manufacturing. Hemicellulose is chemically a xylan, a long polysaccharide molecule consisting of D-xylose units. Xylans (which in turn are examples of so-called pentosans) are typically present in certain hardwoods (such as birch and beech), rice, oat, wheat and cotton seed hulls, various nut shells, straw, corn cobs and stalks, sugar cane bagasse, etc. According to this terminology, pentosans are polysaccharides consisting of five-carbon pentose sugars, such as D-xylose. (Glucans consist of six-carbon D-glucose units, and represent spesific hexosans, important in the growth of dental plaque.) In the manufacturing process of xylitol (2), the xylan molecules are first hydrolyzed into D-xylose. The latter is chemically reduced to xylitol which can be separated by large-scale column chromatography. Xylitol is finally crystallized. The entire process is complicated and demands great engineering skills and experience. The amounts of xylitol present freely in plants are too low for industrial exploitation. Xylitol can, of course, be synthesized by means of organic chemical procedures, but the usage of D-xylose as a starting material is currently more feasible. Xylitol can also be made by means of bacterial fermentations which utilize D-xylose, D-glucose, or other suitable raw materials as substrates. These processes have not been economically feasible.

## 2. The chemical profile of xylitol; terminology

Xylitol is a natural sugar alcohol of the pentitol type, i.e. the xylitol molecule contains five carbon atoms and five hydroxyl groups. Therefore, xylitol can be called a pentitol. Xylitol belongs to the polyalcohols (polyols) which are not, strictly speaking, "sugars" which traditionally include certain nutritive carbohydrate sweeteners (sucrose, corn sugar, corn syrup, invert sugar, D-fructose, D-glucose, etc.; in some reports the term "sugars" is collectively used to refer to mono- and disaccharides). However, the legitimacy for including polyols in the sugar field results from biochemical relationships; polyols are formed from, and can be converted to, sugars (i.e. aldoses and ketoses). Some chemical encyclopaedias define sugars as crystalline, sweet carbohydrates. The sugar alcohols thus fall in this category.

To fully understand the dental effects of xylitol, it is important to refer to the structural differences between various dietary polyols (3). Sorbitol is another sugar alcohol, a hexitol type of polyol, owing to its 6-carbon structure. Because of this, sorbitol can support the growth of cariogenic mutans streptococci and other oral bacteria which are not normally able to utilize xylitol for growth. Because of evolutionary expediency, cariogenic organisms prefer 6-carbon ("hexose-based") structures, such as D-glucose, as an energy source. Therefore, it is important to acknowledge the inevitable biochemical differences between xylitol (a pentitol and pentose-derived) and sorbitol (a hexitol and hexose-derived), and to understand the nomenclature-related definitions described above.

In spite of the existence of some differences between the various sugar alcohols, xylitol and most other polyols also display dentally interesting common properties: they can form certain type of complexes with calcium and certain other polyvalent cations. Such Ca-xylitol complexes can be present, for example, in the oral cavity and in the intestines. In the former, such complexes may contribute to the remineralization of demineralized enamel and dentine caries lesions observed in subjects who habitually consume xylitol. In the intestines, those complexes can facilitate the absorption of calcium through the gut wall; this effect has been suggested to play a role in the xylitol-associated prevention of osteoporosis in experimental animals (4). From the dental point of view, the role of xylitol (and certain other polyols) as stabilizers of the salivary calcium and phosphate ions may

be important. It is possible that xylitol stabilizes the calcium phosphate system present in saliva in the same manner some salivary peptides (such as statherin) do (5).

Xylitol is about twice as sweet as sorbitol. When eaten in solid or crystalline form (such as in chewing gum), xylitol gives a pleasant cool and fresh sensation owing to its high endothermic heat of solution. The caloric content of xylitol is approximately the same as that of "sugar"; in practice, however, xylitol, when eaten as part of a mixed diet, may provide somewhat less calories than sugar.

## 3. Metabolic features of xylitol

For the understanding of the oral safety of xylitol, one has to briefly describe the human metabolism of this carbohydrate. Xylitol is a natural intermediate product which regularly occurs in the glucose metabolism of man and other animals, and also in the metabolism of several plants and micro-organisms. As a result of the ease with which it is converted in the metabolism, xylitol has a low steady-state concentration in human blood. In man, the normal blood xylitol level ranges between 0.03 and 0.06 mg per 100 ml. The excretion of xylitol in the urine is approximately 0.3 mg per hour; there is normally no significant difference in this sense between healthy and diabetic subjects.

In man, ingested xylitol and sorbitol are absorbed through the gut wall at virtually the same rate, and appreciably more slowly than D-glucose and D-fructose. Both polyols are absorbed passively. In most healthy subjects, an adaptive increase in the activity levels of an enzyme (a non-specific polyol dehydrogenase) greatly increases the rate of xylitol absorption in a few days. This is not the case with sorbitol. In unadapted subjects xylitol doses of about 0.5 g per kg body weight may result in transient soft stools (osmotic diarrhoea). Xylitol is slowly absorbed from the digestive tract owing to the absence in the intestinal mucosa of a specific transport system for xylitol. Consequently, about one third of the ingested xylitol (when large single doses are taken in) is absorbed, subsequently entering the hepatic metabolic system. The other two thirds of the ingested xylitol will reach the distal parts of the intestinal tract where xylitol will be broken down by gut bacteria. The end products are mainly short-chain fatty acids, most of which will normally be absorbed and utilized by the body. When very small quantities of xylitol are consumed (as in one piece of chewing gum), it is possible that proportionally larger amounts are directly absorbed.

After appropriate adaptation, xylitol has been administered to human subjects in amounts of 200 g and higher per day without diarrhoea occurring. In practice, usually not more than 50-70 g daily, spread evenly throughout the day, should be given. Dentally effective quantities may vary between about 1 and 20 g per day, preferably between 6 to 12 g. Owing to the slow absorption of xylitol, it has sometimes been characterized as "glucose with delay", a property that can be advantageous in certain clinical situations. Premature infants possess full capacity to metabolize xylitol.

Xylitol supplies large amounts of liver glycogen, or primarily D-glucose. Xylitol is oxidized to carbon dioxide and water by the normal, physiologic pathway of carbohydrate breakdown. About 85% of the xylitol turnover in the body takes place in the liver. About 10 % is metabolized extrahepatically in the kidneys, and the small remainder is used up by blood cells, the adrenal cortex, lung, testes, brain, fat tissue, etc. These figures are similar regardless of the way of administration, i.e. whether oral or by the intravenous route. There is a small difference between endogenous ("natural") xylitol and that which is supplied from outside, for example, when a xylitol-containing diet is consumed. Endogenous xylitol is the physiologic intermediate product from D-xylulose and L-xylulose (these are the keto-sugars corresponding to xylitol). This reaction takes place in the mitochondria catalyzed by enzymes which are specific for xylitol. By contrast, exogenous (ingested) xylitol is slowly absorbed, and eventually enters the portal circulation and the liver where it is dehydrogenated in the cytoplasm of the liver cells by the above mentioned non-specific polyol dehydrogenase enzyme which can also act on sorbitol. This enzyme is a key enzyme in xylitol metabolism and largely determines the metabolic rate of xylitol. When xylitol is given for a few days, an adaptation takes place: the enzyme's levels are increased so that the metabolic capacity of a subject who is accustomed to xylitol, is appreciably augmented.

Because xylitol occurs naturally in agricultural and forest products, xylitol also occurs in various foods used by man. The dietary sources containing relatively high quantities of xylitol are plums, raspberries and cauliflower (0.3 to 0.9 g per 100 g dry matter; the quantities vary depending on the season and they also vary between plant varieties). The presence of free xylitol in food indicates that man and certain domestic animals have consumed xylitol during their entire evolution. In humans, relatively large amounts of xylitol (viz. 5 to 15 g/day) are formed as a metabolic intermediate product of carbohydrate metabolism.

In conclusion, xylitol, D-fructose and sorbitol are converted into D-glucose and various metabolites of D-glucose in the intermediate metabolism, and thus brought into the main stream of carbohydrate metabolism, and either stored as glycogen, oxidized to carbon dioxide and water, or used as building material for the biosynthesis of substances such as lipids. Because of the slow absorption rate, the metabolic capacity is never exceeded when xylitol is administered by mouth.

The usage of xylitol as a sugar substitute has the following physiologic advantages:

(a) Xylitol has a pleasant taste and a sweetness which equals that of sucrose.

(b) With correct xylitol dosage, carbohydrate tolerance is increased.

(c) Small xylitol doses stabilize the metabolic situation in unstable diabetics.

(d) Xylitol has antiketogenic properties.

(e) Xylitol is non- and anticariogenic.

## 4. Oral and metabolic safety of xylitol

Studies in humans and rodents have shown that xylitol, when appropriately administered orally with adaptation, is well tolerated and safe to levels of at least 90 g/day, with no subjective or objective adverse findings. Somewhat less insulin is released into the blood during xylitol administration than during glucose administration.

The oral and metabolic safety of xylitol has been assessed by various international and national regulatory authorities. For example, in 1983 the Joint Expert Committee on Food Additives (JEFCA) of two United Nations agencies (FAO and WHO) allocated an "Acceptable Daily Intake" (ADI) definition "not specified" for xylitol. This indicates that no special consumption limits were needed for xylitol. In detail, JECFA recommended:

> (a) An unlimited ADI based on the safety of xylitol. This type of specification reflects the safest category this Committee can place a food additive. The specification is comparable to that of sorbitol.
>
> (b) No additional toxicological studies were recommended.

Of the numerous positive public health evaluations of xylitol one should mention the FASEB report of the year 1986. FASEB (Federation of American Societies for Experimental Biology) reports are based on comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in relevant areas of biology and medicine. In 1986 FASEB's expert panel completed a report on the health aspects of sugar alcohols and lactose. Based on the comprehensive body of scientific information, the FASEB report concluded that:

> (a) No significant safety concerns would be expected from use of xylitol in humans, and that
>
> (b) Xylitol appears to have the same safety profile as other sugar alcohols, such as sorbitol and D-mannitol.

As a further proof of xylitol's metabolic safety, one should mention the traditional use of xylitol as a source of energy in infusion therapy. Especially German and Japanese physicians have with great success used xylitol,

in combination with other carbohydrates and amino acids, for this purpose. This practice is based, among other things, on the non-involvement of insulin in the initial utilization by the human cells of xylitol, and on the ability of xylitol to exploit several metabolic "entrances" into the liver, compared, for instance, with sorbitol which biochemically speaking has only one "entry point" into the metabolism.

Xylitol has long been used as a sweetener in the diabetic diet; diabetic patients have been found to consume up to 70 g xylitol per day without any adverse reactions. As discussed below, these xylitol levels by far exceed those recommended for dental purposes. The public health evaluation of xylitol has been in greater detail reviewed elsewhere (6).

As already stated above, it is necessary to make a clear difference between the oral (enteral) and parenteral administration of xylitol. Although metabolic studies indicate that the capacity of the human body to turn over xylitol is substantial, the oral consumption of xylitol will never lead to blood xylitol levels that would be too high. This results from the slow absorption rate of xylitol through the gut wall. This indicates that too high oral doses may cause transient osmotic diarrhoea. The laxative effect of large single doses of xylitol is indeed the only adverse effect reported in studies dealing with oral administration of xylitol. Similar effects can be caused by other polyols, and also by D-fructose and lactose (milk sugar). Field experience indicates that humans tolerate xylitol better than sorbitol and D-mannitol. In conclusion, scientific articles and clinical studies have shown, that the gastrointestinal effects of xylitol occur at levels that are much higher than those needed to achieve the dental benefits, such as those used by diabetic patients.

Based on the scientific and public health evaluations, xylitol has been approved in virtually all industrialized countries to be used in oral hygiene products and in other products to promote oral health. Typical dentally beneficial xylitol products are chewing gums, lozenges, dragées and hard caramels. In reality, the range of xylitol products for consumer and other uses has been much broader. In view of the above developments, it is important to acknowledge the recent resolution made in Japan regarding xylitol. The Japanese Ministry of Health and Welfare finished in 1996 a long-term scientific evaluation of xylitol and approved, in spring 1997, xylitol officially as a safe food additive in Japan. This positive public health-related decision will most likely greatly accelerate the development of oral health-promoting xylitol products in Japan and its neighbouring countries.

## 5. Some potential future uses of xylitol

Owing to the molecular properties of xylitol, it will most likely have new biologic, dietary and medical applications in the future. One promising approach is the possible use of xylitol as a dietary agent to prevent mid-ear infections in young children. This effect is based on the growth inhibition by xylitol of alpha-hemolytic streptococci, including Streptococcus pneumoniae. As one consequence of this, the usage of xylitol chewing gum by young day-care center children was shown to reduce the occurrence of acute otitis media and antimicrobial treatment received during the gum-using period (7). It is possible that the virulent bacterial flora present in the entire aero-digestive tract of man can be favourably affected by systematic xylitol use. Xylitol, by virtue of its pentitol nature, modifies the outer environment of selected pathogenic organisms and the outer structures of the organisms themselves. Such changes may result in a lowered ability of the organisms to adhere onto epithelial cell surfaces and other host tissue surfaces, reducing the risk of infection. It is clear, however, that the above otitis media-related observations must be verified by independent studies before further conclusions can be made.

## 6. Xylitol compared with other sweeteners

The following treatise will be restricted to deal with differences between dental and oral biologic effects of some common dietary sweeteners. Therefore, the "sugar alcohol nature" of xylitol must be emphasized. For a better understanding of the dental effects of xylitol, one has to recall the chemical features of the xylitol molecule

described above. All dietary sugar alcohols share several common properties that make them biologically unique. Some of them are as follows:

(a) The absence of reducing carbonyl group. This makes sugar alcohols chemically somewhat less reactive than corresponding aldoses and ketoses; some of the sugar alcohols are, therefore, less capable of supporting plaque growth.

(b) The reducing power. Regardless of the above relative inertness of polyols in the human oral cavity, some sugar alcohols may actively participate in metabolic reactions where their "extra" hydrogen atoms can be deposited on other metabolites, to form other reduced products of metabolism, which are less harmful to the tooth structure.

(c) Complex formation. As stated above, sugar alcohols can form complexes with Ca and certain other metal cations, thereby possibly affecting the metabolism of those cations in the oral cavity. Consequently, some sugar alcohols may contribute to the physiologic remineralization reaction whereby calcium phosphate salts are deposited in calcium-deficient sites.

(d) Protein stabilizing effect. Sugar alcohols can protect proteins in aqueous solutions against denaturation and other damage. It is thus possible that, for example xylitol, protects salivary proteins.

As a result of evolutionary expediency, human cariogenic bacteria have developed effective enzyme systems which utilize the chemical energy present in some ubiquitous dietary carbohydrates. Those carbohydrates are normally based on six-carbon skeletons (or multiples thereof) and normally have an aldose or a ketose structure. Suitable examples of such sugars are D-glucose, D-fructose (which are six-carbon monosaccharides) and sucrose (which is a disacacharide consisting of D-fructose and D-glucose). Starch consists of long chains of D-glucose molecules, and can be broken down in the oral cavity by plaque and salivary enzymes to yield D-glucose. All simple dietary sugars (the above three serve only as examples) may produce acids and may serve as building material in the formation of adhesive plaque polysacharides (glucans were above mentioned as an example of such molecules). Sucrose, D-glucose and D-fructose are normally in this sense effectively utilized by cariogenic bacteria. The upshot of this utilization can be the formation of potently cariogenic plaque. Xylitol is unable to form such plaque because the xylitol molecule contains only five carbon atoms. For the same reason, xylitol does not produce lactic acid.

No study has shown that the oral bacteria become adapted to utilize xylitol for effective acid and polysaccharide production. Sorbitol, on the other hand, has been shown to stimulate plaque growth; adaptation to sorbitol occurs. Sorbitol itself does not give rise to large amounts of lactic acid in human dental plaque, but the ability of sorbitol to promote the growth of cariogenic streptococci makes it indirectly caries-promoting. (However, sorbitol is by far safer from the cariologic point of view than sugar.)

It is irrational to compare xylitol with artificial, intense sweeteners (such as saccharin, cyclamate, aspartame, etc.), because these substances are used at totally different chemical concentrations in food. The synthetic sweeteners´ chemical activity is, therefore, so low in most foods that they rarely exert any specific, significant, oral health-promoting effects. Xylitol, being a natural dietary carbohydrate, must be used at chemical levels corresponding to those of regular table sugar. Such concentrations are more likely to display specific effects on oral micro-organisms and on oral tissues.

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