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A current and global review of sweeteners; regulatory aspects

J. M. García-Almeida[1], Gracia M.ª Casado Fdez.[2] and J. García Alemán[1]

[1]*Specialist in Endocrinology and Nutrition.* [2]*Degree in Human Nutrition and Dietetics. UGC Endocrinology and Nutrition. Hospital Virgen de la Victoria. Malaga. Spain.*

Abstract

In this chapter we review the role and potential benefits of non-caloric sweeteners, as part of the diet. After appearing and interest in the beneficial effects attributed to them, face different situations and conditions (obesity, diabetes...), more and more numerous studies, show their ineffective use.

In conclusion, further research and results are needed to provide convincing evidence of their long-term effectiveness and the absence of negative effects from their use.

The interest of the chapter lies in examining the distinctive aspects of sweeteners compared with sugar, measured as the standard of comparison. We will focus then on the other substances that are commonly used to sweeten foods instead of sugar.

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Key words: *Artificial sweeteners. Sugar and sugar substitutes. Nonnutritive sweetener. No caloric sweetener. Glycemic response.*

UNA VISIÓN GLOBAL Y ACTUAL DE LOS EDULCORANTES; ASPECTOS DE REGULACIÓN

Resumen

En este capítulo revisamos el papel y los posibles riesgos/beneficios de los edulcorantes como parte de la alimentación. Tras su aparición e interés por los efectos beneficiosos atribuidos a los mismos, frente a diferentes situaciones y patologías (obesidad, diabetes, caries, etc.), cada vez son más numerosos, sin embargo, los estudios que parecen constatar la ineficacia de su uso. Por tanto, se requieren más investigaciones que aporten datos convincentes de su efectividad a largo plazo, así como de la ausencia de efectos negativos, derivados de su uso.

El interés del capítulo reside en examinar los aspectos distintivos de los edulcorantes frente al azúcar, considerándose ésta como patrón de comparación. Nos centraremos pues, en las otras sustancias que habitualmente se utilizan para edulcorar los alimentos en lugar del azúcar.

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Palabras clave: *Edulcorantes artificiales. Azúcar y sustitutivos del azúcar. Edulcorantes no nutritivos. Edulcorantes acalóricos. Respuesta glucémica.*

Abbreviations

ACS: The American Cancer Society.
ADA: The American Diabetes Association.
AHA: The American Heart Association.
APM: Aspartame.
mRNA: Messenger RNA.
DM: Diabetes Mellitus.
HIS: High-intensity sweeteners.
MS: Member states.
EFSA: European Food Safety Authority.
FFQ: Food-frequency questionnaire.
FOS: Fructooligosaccharides.
GIP: Glucose-dependent insulinotropic peptide.
GLP: Glucagon-like peptides.
GRAS: Generally recognised as safe.
ADI: Acceptable daily intake.
EDI: Estimated daily intake.
GI: Glycaemic Index.
BMI: Body mass index.
JECFA: Joint FAO/WHO Expert Committee on Food Additives.
NNS: Non-nutritive sweeteners.
WHO: World Health Organisation.
SCF: The EU Scientific Committee on Food.
EU: European Union.

Corresponding author: José Manuel García Almeida.
Hospital Virgen de la Victoria.
Endocrinology and Nutrition Unit.
Campus de Teatinos, s/n.
29010 Malaga. Andalucía. Spain.
E-mail: jgarciaalmeida@yahoo.com

Introduction

The term 'sweetener' refers to those food additives which are able to mimic the sweetness of sugar and which usually provide less energy. Some are natural extracts whilst others are synthetic. In the case of the latter they are also known as artificial sweeteners. The use of non-caloric sweeteners, as a substitute for all or part of the sugar content in food and drink, has experienced its biggest growth over the past 35 years[1] and projected sales for 2014, according to a recently published systematic review, are expected to exceed one billion[2].

New eating patterns, characterised by the high consumption of processed foods, with changes involving their fat and sugar content, mark a notable shift away from the traditional Mediterranean diet. In this respect, there has been an exponential growth both in energy-rich foods and those that are supposedly low-calorie. Industry pressure plays a pivotal role in these food consumption patterns. It is therefore essential to clarify the effectiveness and safety of these substances so that consumers can be provided with clear information.

Considering 77% of all calories consumed in the USA, from 2005 until 2009, contain caloric sweeteners and there is a trend toward consuming non-caloric sweeteners, it's vital to conduct extensive research and to take a strict regulatory approach on these issues. There are currently no conclusive data on the effects of sweeteners on crucial factors such as energy intake, appetite and their relationship with the sweet taste and, furthermore, the exact quantities of these sweeteners that foods contain are unknown. For this reason, it would be of great interest to quantify, as accurately as possible, the prevalence of consuming products containing non-caloric sweeteners. This article tries to summarise the current principal scientific and legislative findings on this issue with an eye to improving the rational use of these substances in our diet[3].

The concept of health is very broad and its determinants encompass biological aspects, such as genetic characteristics, and other socio-economic and cultural aspects which, as a whole, determine an individual's health status (Fig. 1). Over time, changes in disease patterns, probably associated with lifestyle changes in the general population, have led to an increase in the incidence of many chronic diseases such as obesity, type II diabetes, and metabolic syndrome, which ultimately result in an increase in cardiovascular morbidity and mortality. Interest in the potential role of sweeteners has grown, due to the need to find alternatives to prevent disease and maintain good health by following a healthy diet.

Obesity has become one of the biggest global health challenges of the 21st century. The increase in childhood and adolescent obesity is particularly alarming given its association with metabolic diseases and their cardiovascular complications. The people of developing countries are experiencing rapid changes in their eating habits as well as increases in the rates of childhood obesity. The considerable increase in sugary drink consumption among adults and children in the USA and other countries is regarded as a potential contributor to the obesity pandemic. Recent evidence shows that sucrose consumption in drinks is approaching 15% of the American public's daily caloric intake, accounting for up to 357 kcal per drink. All this has resulted in the development of regulatory strategies which limit the sale and, consequently, the consumption of these drinks.

Several randomised and controlled studies have been published in *The New England Journal of Medicine*4 which provides a basis on which to promote the development of health recommendations and government/political decisions aimed at limiting sugary drink consumption, particularly those which are served at a low cost and in over-sized portions, with a view to reversing the growth in childhood obesity. In these studies the use of sugar was limited, substituting it for lower-calorie sweeteners. Interventions of this kind, if proven safe and effective, could help to prevent young people from developing type II diabetes and its complications.

Besides the interest generated by their potential preventative role in the development of chronic metabolic disease, we could also highlight their effect on diseases of the oral cavity such as tooth decay. In particular, polyalcohols can reduce the risk of tooth decay. For example xylitol is considered to be cariostatic and helps to prevent tooth decay[5].

Therefore, and from the perspective of sweetener consumption, survey data confirms that they are currently looking to use non-caloric sweeteners with a view to reducing the total caloric intake, promote weight loss and/or prevent the development of diseases like diabetes or tooth decay. However consumers are also concerned about the risk associated with their use, such as 'artificial or natural' elements and whether they pose a risk to health.

The estimated consumption of sweeteners is complex but it would appear that there are more than 6000 ready made products which contain them in the USA, mainly soft drinks. Information on nutrition labels is often incomplete, without any details on the exact amount. Data from NHANES 2007-2008 24-hour recalls and food frequency questionnaires show an increase in the American population's consumption of sweeteners which, interestingly, is not associated with a reduction in sugary foods.

With regard to the legal aspects of the use of sweeteners at a European level, the European Parliament and Council Directive 94/35/CE of 30th June 19946 on all sweeteners for use in foodstuffs arose as the initial

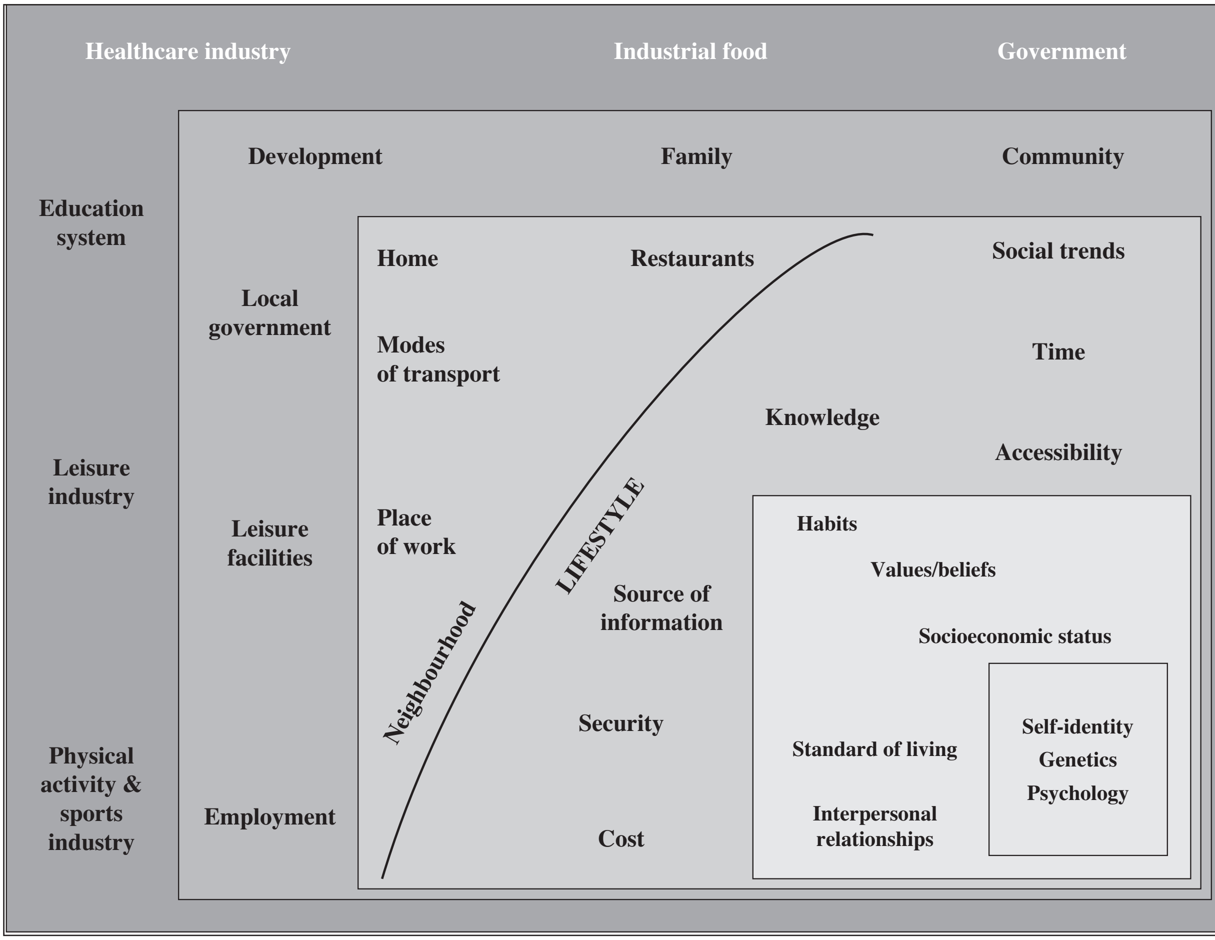

Fig. 1.—Global determinants of health: The multifactorial relationship between individuals and environmental factors, in relation to food choices and healthy behaviour. Amended by Anderson GH, Foreyt J, Sigman-Grant M, Allison DB. The use of low calorie sweeteners by adults: impact on weight management. J Nutr 2012; 142 (6): 1163S-9S.

governing regulation. It is a specific directive from the Framework Directive on food additives used as sweeteners. The articles of this law contain explanations and specific provisions for the use of sweeteners in food and drinks. The maximum usage levels for each of the low calorie sweeteners are set out in specific food categories in the Directive's annex. Over the years, this Directive has been amended three times to accommodate technological advances in the field of sweeteners. Later on, the European Parliament and Council adopted a regulatory framework (Regulation No.1333/2008) which, from January 2011, consolidated all the existing authorisations for sweeteners and food additives into a single legal text. At present, the following low calorie sweeteners are authorised in the European Union (EU): Acesulfame-K (E950), Aspartame (E951), Aspartame-Acesulfame salt (E962), Cyclamate (E952), Neohesperidin dihydrochalcone (E959), Saccharin (E954), Sucralose (E955), Thaumatin (E957) and Neotame (E961)[7] (International Sweeteners Association at http://www.info-edulcorants.org/ es/recursos-profesionales/folleto-isa).

Following the EFSA's favourable opinion use of stevia derivatives, steviol glycosides, were finally approved as a natural non-caloric sweetener throughout the European market. They can be used as food additives and thereby provide a healthy and natural alternative for sweetening foods, especially for diabetics or those who wish to stay in shape, for example: flavoured drinks or diet foods designed for weight control).

Annex II to Regulation (EC) No. 1333/2008 of the European Parliament and Council was amended with the introduction of the Commission's Regulation (EU) No. 1131/2011 of the 11th November 2011, with regards to steviol glycosides (E960) and limits on the use of sweeteners in different foods and drinks were established (soft drinks, fermented dairy products, flavoured ice creams, table sweeteners, diet products for weight control.)

The safety of sweeteners is evaluated by the national authorities, the EU Scientific Committee on Food (SCF) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The SCF was responsible for it from 1974 until 2003, the year in which it became the responsibility of the European Food Safety Authority (EFSA) (http://efsa.europa.eu/). Within the EFSA, the Scientific Panel on Food Additives and Nutrient Sources (ANS) is currently responsible for the regulation of these substances[8].

Legal aspects need to be reviewed on a continual basis to update new scientific developments published on the safety or effective use of sweeteners. As they are very diverse molecules, there are numerous potential risk sources: interference with absorption, metabolism or the excretion of any intermediate metabolite, as well as any allergic reaction, accumulation in tissues, effects on normal intestinal flora, changes in blood sugar regulation, or interaction with other pharmaceuticals or drugs.

The European Food Safety Authority (EFSA) has recently produced a scientific evaluation of the safety of aspartame. In order to carry out this comprehensive risk assessment, the EFSA (http://www.efsa.europa.eu/en/press/ news/130108.htm) has carried out a thorough review of the scientific literature on aspartame and its breakdown products, including new studies on humans. In this safety re-evaluation by the EFSA, it was concluded that aspartame does not present any risk of toxicity to consumers at current exposure levels. The current acceptable daily intake (ADI) is considered safe for the general population and consumer exposure is normally below the ADI. When establishing the ADI for aspartame the ANS commission also considered the results of long-term studies on phenylalanine, an aspartame metabolite, both in toxicity and carcinogenesis tests on animals and humans, specifically, the foetal development in mothers who consume this sweetener.

At the same time, in North America the US Food and Drug Administration (FDA) has been responsible for evaluating its safety since 1958 and seven sweeteners have been approved for use in the USA: Acesulfame K, Aspartame, Neotame, Saccharin, Stevia, Sucralose and Luo han guo.

The American FDA regulations also refer to the concept of estimated daily intake (EDI), which is a conservative estimate of the probable daily intake over a lifetime and the concentration of food additives in commonly eaten foods. Another important concept concerning consumer safety is GRAS (Generally recognised as safe), which implies that, although the potential risks aren't yet completely understood, experience through common use has not raised any problems. This is the accepted recognition to market stevia currently in the USA, pending further information in the future.

Information on the correct use of these substances comes from knowing the differences on the nutrition facts labels of commonly consumed products that contain sweeteners. The presence of sweeteners should be listed in the food's ingredients, along with calorie content, fat or carbohydrates, in the nutritional labelling information.

However, with the exception of warnings about phenylalanine from aspartame or the amount of saccharin, this information is usually missing or incomplete. It opens up a major area for improvement in the field of sweetener use, to provide consumers with the best information in the future. Scientific research, although limited in humans according to the Evidence Analysis Library of the Academy of Dietetics and Nutrition (http://www.adaevidence library. com/files/Docs/NNSResourceDraft3.pdf), shows that artificial sweeteners are safe to use for the general population, including pregnant women and children. Most studies have not found any adverse effects related to the consumption of sweeteners, even when they are consumed in large quantities. Special population groups, such as pregnant women, should limit their use even though they have been approved by the FDA, using them in moderation.

In this chapter we will review the main sweeteners, their metabolic effects and we will analyse their potential strengths, weaknesses, opportunities and threats (SWOT system).

Sweeteners: types and key characteristics

With regard to overall classification, given the large variety of the existing types, sweeteners can be grouped according to their calorie content (caloric or non-caloric), their source (artificial or artificial) or even their chemical structure (Fig. 2). Naturally sourced sweeteners are not necessarily safer or more effective and, in this respect, there is a great deal of consumer misinformation about them. There are a wide variety of sweetening substances. In this chapter we will focus on the most common ones and those with existing scientific studies which are of interest. The current classification of the main sweeteners is presented in table I.

Sugars are carbohydrates and therefore contain 4 calories per gram. They are found naturally in many foods such as fruit, vegetables, cereals and milk. As with starches, if good oral hygiene is not maintained they can be harmful to teeth, although the most recent scientific literature also points out that the stickiness of food and the frequency with which these foods are consumed could have an impact on levels of tooth decay. Sucrose has a moderately high glycaemic index (GI). Other natural caloric sweeteners, like honey and maple syrup, are older, contain sugar, but they also have other nutritional qualities. Their glycaemic index is somewhat lower than sugar. Saccharins are included in the group of natural sweeteners, among which the most commonly used are sucrose, fructose, glucose (GI of 100 and a sweetness relative to sucrose of 0.5-1) and maltose (GI 105 and a sweetness relative to sucrose of

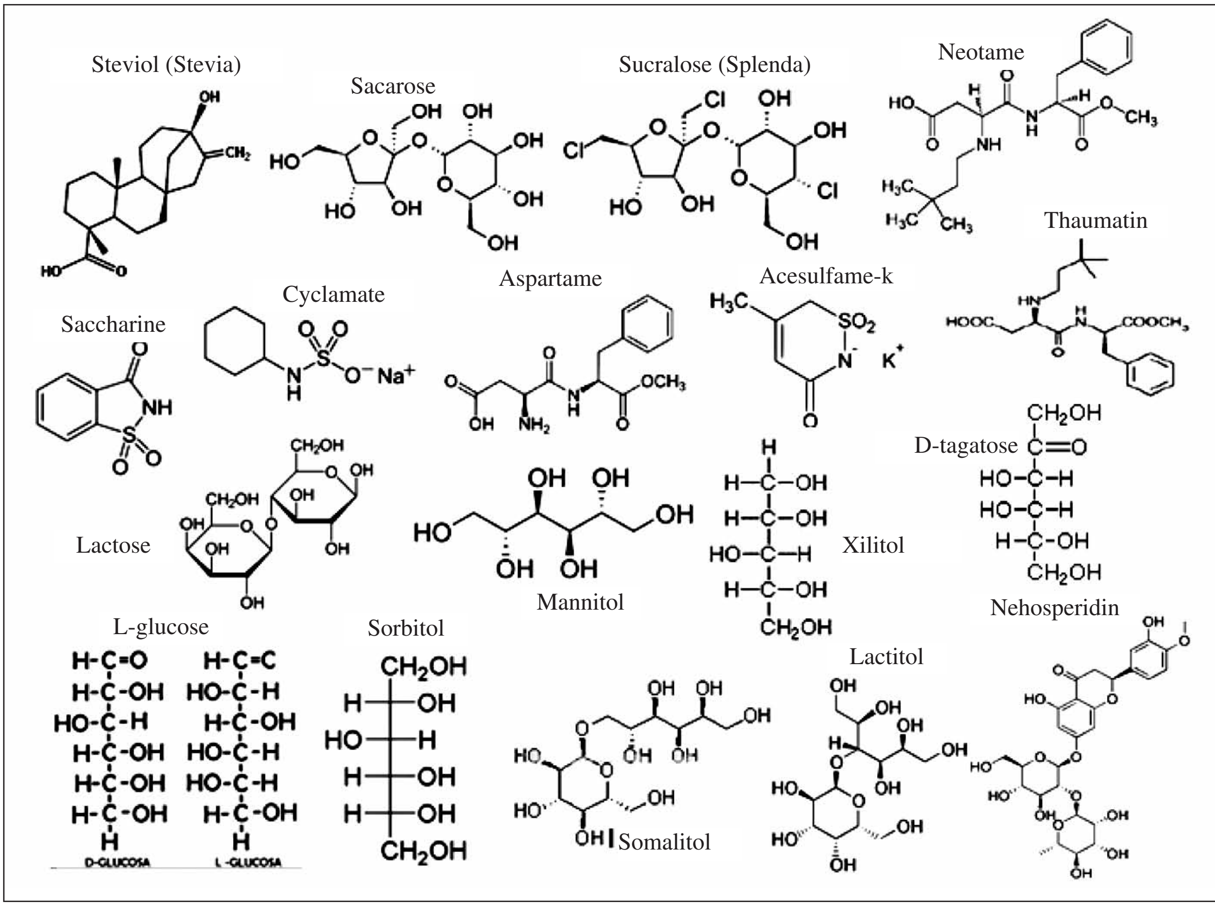

Fig. 2.–The chemical structure of sweeteners.

Table I
Classification of sweeteners

Caloric	Natural	Sugars	Sucrose, glucose, dextrose, fructose, lactose, maltose, galactose and trehalose, tagatose, Sucromalt*
		Natural caloric sweeteners	Honey, maple syrup, palm or coco sugar and sorghum syrup
	Artificial	Modified sugars	High fructose corn syrup, caramel, inverted sugar
		Sugar alcohols	Sorbitol, xylitol, mannitol, erythritol maltitol, isomaltulose, lactitol, glycerol
Non-caloric	Natural	Non-caloric sweeteners	Luo Han Guo, stevia, thaumatin, pentadin, monellin, brazzein
	Artificial	Sweeteners	Aspartame, sucralose, saccharin, neotame, acesulfame-K, cyclamate, neohesperidin DC, alitame, advantame

* Calorific value similar to fructose, although it really is an artificial oligosaccharide.

of 0.5). Fructose is typically used as a substitute for sucrose in diabetic patients and as a sweetener in the manufacture of many products labelled as 'suitable for diabetics'. However, recently it has been proven that diets high in fructose, especially if it is added to manufactured foods, can cause hyperinsulinaemia, hypertriglyceridaemia and insulin resistance, which was a determining factor in the recommendation that diabetics should limit its use. Its properties include a calorie content of 4 kcal/g, a GI of 23 and a sweetness relative to sugar of between 1 and 2. On the other hand, tagatose and trehalose have different calorie contents, 1.5 and 3.6 and a sweetness of 0.9 and 0.45 respectively.

Fructooligosaccharides (FOS) have half the calories per gram than sucrose or glucose with a sweetness relative to sucrose of 0.3-0.6. Inulin is a fructan with a degree of polymerisation of 20 to 60 fructose monomers and a documented prebiotic effect, which is found naturally in a native Andean tuber, the yacon (12.5g/100g), and which had historically been grown in various Latin American countries. This tuber is mainly used as a sweetener and the possibility that it has nutraceutical properties due to its high content of various minerals, vitamin C and B group vitamins. Coco sugar is another traditional product which can be used as an alternative to sugar in diabetic patients as it is a food which is considered to be low GI. It consists of sucrose, aminoacids such as glutamine and stands out for its high mineral and group B vitamin content.

Alcohols derived from sugar are also carbohydrates which are produced naturally, although in small amounts, in plants and cereals. They generally contain less calories per gram than sugar and are not associated with tooth decay. Despite the fact that they are carbohydrates, the body can't fully metabolise them and, consequently, they tend to have less than 4 calories per gram and a very low glycaemic index. Some of the carbohydrates used as sweeteners (i.e. polydextrose or xylitol) have been proposed as ingredients for functional foods useful for controlling intake because of their low energy content, which is due to their partial metabolism (1.5 to 3 kcal/g) and also the possible effects of some of them on appetite suppression, although the clinical of this is not yet known. A large number of these are increasingly used as sweeteners in 'sugar free' products. The chemical structure of these substances (Table II) cause them to have greater sweetening powers when they interact with taste receptors and a lower absorption by the digestive tract, consequently they have a lower usable calorie content than sugar. Limits on the amount consumed are related to their secondary gastrointestinal effects.

The manufacture of sugars modified by enzymatic starch conversion, which are frequently used in industrial cooking or in processed foods, gives rise to a blend of carbohydrates which are usually high in calories and have an elevated glycaemic index. One product regularly used in the industry which belongs to this group and has a nutritional value close to 4 kcal/g, typical in carbohydrates, is high fructose corn syrup with a relative sweetness of 1.

Sucromalt is an artificial oligosaccharide (http://www.aesan.msc.es/AESAN/docs/docs/cadena–alimentaria/tabla_decisiones_2013.pdf) which is converted from sucrose and maltose, to fructose and an glucose oligosaccharide with links at 1-3 and 1-6 alternatively. It has been extensively used in the design of

Table II
Description of sugar alcohols

Sugar alcohols	*Nomenclature*	*Nutritional value (kcal/g)*	*Sweetness, relative to sucrose*	*Maximum tolerable quantity without gastrointestinal symptoms (g/day)*	*Presence*	*GI*
- Erythritol	E968	0.2	0.75	At higher doses	In fruits and other fermented foods	1
- Hydrolysed hydrogenated starch (Lycasin) Polyglycitol Syrup	E964	≤ 3	0.4-0.9	–	Sports drinks (e.g.: powerade), ice cream	–
- Lactitol	E966	2	0.5	≥ 20	Sweets, biscuits, ice cream	3
- Maltitol	E965	2.1	1	30-50	Chewing gum, sweets jelly sweets	35
- Manitol	E421	1.6	0.7	10-20	Chewing gum*	2
- Sorbitol	E420	2.6	0.5-1	> 80	Chewing gum*	4
- Xilitol	E967	2.4	1	> 50	Chewing gum, breath mints, toothpaste and mouthwash	12

* Furthermore it also contains isomalt, aspartame, and acesulfame-K. They amount to 61.7g of polyalcohols/100 g.

low GI foods. Its nutritional value is similar to fructose and its sweetness relative to sucrose is 0.7.

There are also natural sweeteners (Stevia, Luo Han Guo, Thaumatin and Brazzein) whose calories are insignificant compared to the quantities usually used for sweetening purposes. These are not carbohydrates, therefore they don't have a glycaemic index. They are considered high-intensity sweeteners (HIS).

Stevia, is probably one of the sweeteners which has generated the most interest in scientific and informative forums over the past few years. It is used as a sugar substitute and it has a slow taste onset at the beginning and is longer lasting, although in high concentrations it can have a bitter taste similar to 'liquorice'. Although the word 'stevia' refers to the whole plant, only certain parts of the stevia leaf are sweet. These sweet components are known as steviol glycosides (an alcohol which can be naturally found in the plant). Furthermore, the term 'stevia' typically refers to a crude preparation (whether it's powder or liquid) made from the plant's leaves and these preparations contain a mixture of various components, not just those that give the leaf its sweet flavour.

Steviol glycosides are the sweet components of the stevia leaf and there are several types, although the most common are stevioside and rebaudioside A. Stevioside is the most common steviol glycoside in the stevia leaf and has been widely studied. On the other hand, rebaudioside A is a better tasting steviol glycoside and is metabolised in the same way as a stevioside. These sweeteners are up to 480 times sweeter than sugar. Their leaves are naturally 15-30 times sweeter than sugar. It is a natural product which has a glycaemic index of zero and is therefore suitable for diabetics. It is heat-stable and suitable for cooking as well as suitable for use in processed foods. It has been used for centuries by the indigenous people of Paraguay, South America and also in Asia (Japan) since the 1970s. Its standardisation in the American market from 2008 onwards with GRAS recognition has proven complicated. The native plant contains proteins, fibre, iron, phosphorus, calcium, potassium, zinc and vitamin A, and its derivatives often provide varying amounts of the active compounds which is a major limitation of their use. Various studies have been conducted to examine their effects on weight, appetite or gut flora with results that are not entirely conclusive, therefore more studies will be needed in the future to clarify this matter.

The EFSA recommended ADI for stevia, or steviol glycosides, is consistent with the level adopted in the past by the Joint FAO/WHO Expert Committee on Food Additives, JECFA).

Luo Han Guo is a non-caloric high-intensity natural sweetener (300 times sweeter than sugar cane) cane). It is extracted from monk fruit, from China, which has been used for hundreds of years. Its sweetness comes from a substance called mogroside in the pulp of the fruit. One of the advantages it has over stevia is the lack of a bitter aftertaste which is characteristic of stevia. Like stevia, its glycaemic index is zero and it has recently been approved by the FDA for use in GRAS recognition for the additives of certain foods from 2010. It's still under evaluation in Europe[5].

One subset of natural sweeteners which is still completely outside of the commercial market is 'sweet proteins'. In spite of the fact that seven sweet proteins have been identified (Thaumatin, monellin, mabinlin, pentadin, brazzein, curculin and miraculin) only two have been commercialised: Thaumatin and brazzein. All of these proteins have been extracted from plants which grow in rain forests. Sweet proteins tend to have lingering aftertastes, a characteristic which clearly distinguishes them from sugar. Thaumatin is the most advanced sweet protein regarding product development and its situation with the regulatory authorities.

'Artificial sweeteners' per se usually refer to the various existing compounds on the market which are characterised by the fact that they are non-caloric, they have no glycaemic effect whatsoever and they are high-intensity sweeteners: This group is of the most interest in the area of research, with the aim of proving their safety and providing firm data on their possible therapeutic effects on patients with diabetes or other specific health problems. At a consumer level interest in these products has increased significantly in the search for low-calorie products (Table III).

Saccharin continues to dominate the global market of HIS for levels of consumption, with millions of tonnes in 2010. Asia continues to be by far the world's biggest consumer of saccharin. Saccharin was the first artificial sweetener which was discovered more than 120 years ago. Like most artificial sweeteners, it was discovered by accident whilst looking for other unrelated substances. It is 300 times sweeter than sugar, but it has a slightly unpleasant metallic aftertaste. It has a glycaemic index of zero, it contains no calories and is suitable for diabetics. It doesn't tolerate high temperatures so it is not suitable for cooking. It blends well with other sweeteners, or even with a small amount of sugar as in some 'diet' or 'zero' drinks.

Cyclamate is the second oldest artificial sweetener in use today. It's the least powerful of this group, only 40 times stronger than sugar. For this reason, it's often blended with other sweeteners like saccharin. It is heat-stable and has a long shelf life which makes it suitable for cooking and food processing. It has a glycaemic index of zero and contains no calories. Like saccharin, it is also widely used in Asia. Its use is authorised in Europe and 50 other countries, but it has been prohibited in the USA since 1969 due to a reported associa-

Table III
Description of sugar alcohols

Sweetener	*Nomenclature*	*Nutritional value (kcal/g)*	*Sweetness, relative to sucrose*	*ADI* (mg/kg weight/day)*		*Maximum amount of sweetener (mg/day) in a 70 kg subject*	*No. of drinks/ over = ADI for a 70 kg subject ****
				EU	*FDA*		
- Acesulfame-K	E950	0	200	0-9	15	630	16/13
- Aspartame	E951	4	160-220	0.40	50	2,800	15/70
- Cyclamate: Cyclamic acid and sodium and calcium salts	E-952	0	30	0-7	Not permitted	490	–
- Lu Han Guo or concentrated fruit extracts (mogroside)	Natural sweetener	0	150-250	Not permitted	Unspecified. Included in GRAS status	–	–
- Neohesperidin DC	E959	0	1,500	0-5	–	350	–
- Neotame	E961	0	8,000	0-2	18	140	Absent in carbonated drinks and not consumed in products
- Saccharin and its sodium, potassium and calcium salts	E954	0	300	0-5	Unspecified	350	44/9
- Stevia (steviol glycoside)	E960	0	300	0-4	4	280	16.5/31
- Sucrose (splenda)****	E955	0	600	0-15	5	1,050	15/95.5
- Thaumatin	E957	approx. 0	2,000-3,000	Unspecified or by JECFA	Not specified. Included in GRAS status	–	–

tion with developing bladder tumours in animal models and has not been reviewed since then.

Sucrose is a modified form of table sugar (sucrose) which has no calories and is 600 times sweeter than sugar. Its flavour is considerably different to table sugar and does not decompose when heated. It is commonly used all over the world, alone or with other sweeteners, and can be found in more than 4,500 foods and drinks.

Neohesperidin dihydrochalcone is a sweetener which is derived from the chemical modification of a substance found in bitter oranges. It is between 250 and 1,800 times sweeter than sucrose and has a longer lasting sweet flavour with a liquorice aftertaste. It has not been approved by the FDA, but it has been in Europe.

Aspartame is an artificial sweetener which is almost 200 times sweeter than sugar. It is a protein and as such, contains 4 calories per gram. However, it is so sweet that only a small amount is needed and so its calorific value is insignificant. It continues to be one of the most commonly used and well-known intense sweeteners, thanks largely to its strong market position in the USA, its main producer, which consumes 60% of the global demand for this substance. It decomposes when heated and is therefore not suitable for cooking. It has almost completely replaced saccharin as the most commonly used sweetener in 'diet' drinks. There have been huge controversies over its safety although agency reports claim that it is safe for consumption. It is the biggest source of complaints to the FDA, more than any other product or medication.

Acesulfame-K is another compound 130-200 times sweeter than sucrose. It is not metabolised and is eliminated unchanged. It's frequently used in soft drinks, fruit nectars, table sweeteners, dairy products, oven-baked goods, toothpaste and pharmaceutical products. There is a combination of aspartame and acesulfame whose composition is 64%-36% respectively. It is known by the E number E-962, has an immeasurable nutritional value and its sweetness relative to sucrose is 350.

Neotame is a dipeptide derived from aspartame and has a sweetness 8,000 times higher than sugar.

Unlike aspartame it doesn't decompose when heated and therefore is suitable for cooking and for use in processed food. It has zero calories per portion and a glycaemic index of zero, which makes it suitable as part of a diabetic diet. It is not metabolised to phenylalanine and so it is safe for phenylketonuria patients. It is mainly used by food manufacturers, in blends with sucrose and other HIS. Since it was introduced to Europe in 2010, its use has grown considerably.

Alitame is 2,000 times sweeter than sugar. It is a dipeptide made from aspartic acid and alanine. It is stable, doesn't have any calories and has a glycaemic index of zero. It has still not been approved in the USA but it has in Europe (E956).

There are many new sweeteners like advantame, a derivative of the same aminoacids as aspartame with vanillin, a component of vanilla. Compared to aspartame (about 200 times sweeter than sugar), advantame is between 20,000 and 40,000 times sweeter than sugar. It has been authorised in Australia and New Zealand, and is considered GRAS as a flavouring for non-alcoholic drinks, chewing gum and dairy products.

The health effects of sweetener consumption

The general and metabolic impact of using these substances, mainly added to food and drinks, can affect the quality of the end product (nutritional and organoleptic properties), energy consumption and body weight.

Before choosing one of these substances for its supposed metabolic effects it should be compared with sugar as a reference standard. However, in reality the current lack of knowledge on these possible effects is very significant, therefore it is difficult to support their use based on scientific evidence which is clearly full of contrasts[2].

In theoretical models these lower calorie substances, which have less of an effect on blood sugar, could have a beneficial impact on weight control or diabetes, however this correlation is unlikely.

Recent results obtained through short-term intervention models show that artificial sweeteners, especially in drinks, may be useful in reducing energy intake as well as body weight and reducing the risk of type II diabetes and cardiovascular disease, if it's compared with sugar consumption. But in order to confirm this specially designed long-term research is needed[9].

A consensus among the organisations has recently been published (the American Diabetes Association - ADA and the American Heart Association - AHA) in order to clarify certain aspects of the effects on appetite and components of cardiometabolic syndrome. There are significant limitations on the interpretation of research data due to inherent difficulties in the design due to isolated modifications of the diet's carbohydrate content but without changing fat or protein content, that is to say, in order to maintain the calorie content proteins or fats have to be increased and this can affect appetite. The majority of data involving humans comes from observational studies and certain randomised controlled trials on changing sweeteners in soft drinks. In many of these studies, the data on sweetener consumption in food frequency questionnaires (FFQ) on their exact composition in the products consumed is not well documented due to incomplete information on labels or industry references on the quantities contained in processed foods. On the other hand, experimental research on animals provides important data on the potential adverse effects or toxicity of sweeteners. However, extrapolation of these results to the general population has major limitations[10].

Sweeteners and energy intake

A priori, it would be logical to think, from an energy intake point of view, that substitution of sugar with lower calorie sweeteners should reduce the total energy consumption. However, this subject is controversial given that scientific research exists with contradictory results. Furthermore, it should also be taken into account that in processed products, not only the sweetness provided by sugar needs replacing but also the physical or other technological properties of sugar. The result is that a product reformulated with less sugar is often higher in calories than the 'full sugar' version because the sugar has been replaced with other higher calorie nutrients, such as fat.

Some studies on humans have shown a short-term reduction in calorie intake resulting from only a partial compensation of compensation of the calories that are not ingested when compared with sucrose, mainly in soft drinks. However, there is also epidemiological data which connects the use of sweeteners with weight gain. It would appear that the dissociation between the sensation of sweetness and the reduced calorie content produced by sweeteners could cause an increase in appetite, giving rise to a higher energy consumption and weight gain. This operative conditioning theory (Pavlov's Model) has been demonstrated in animal models[11].

Observational studies have also described the association of sweetener use with an overall poorer quality diet due to the loss of healthy eating patterns which include fruit and vegetables. There are many associated confounding factors which make it difficult to draw clear conclusions, such as the fact that these low-calorie foods are frequently associated with other higher calorie foods, and individuals choose them precisely in order to reduce their overall calorie intake.

Furthermore, it is known that, both in humans and animals, food consumption causes a thermogenic response in the cephalic phase of digestion. This response prepares the gastrointestinal tract for the arrival of nutrients. There is evidence in rodent models that the chronic use of sweeteners, such as saccharin, causes a reduction in this stimulus and slows down the thermic effect of food, and perhaps other aspects of metabolic equilibrium[11].

It has been proven that sweeteners can play an active role in the gastrointestinal tract by reacting with the sweet taste receptors (T1R family of receptors and a-gustducin), and mediating changes in peptide hormone responses such as glucagon-like peptides (GLP) in intestinal L cells. It has therefore been hypothesized that the concomitant intake of artificial sweeteners together with food or drinks containing sugar could enable faster absorption of sugar, as well as enhancing GLP-1 and insulin secretion, affecting weight, appetite and blood sugar[12].

Sweeteners and appetite regulation

The mechanisms that sweeteners can use to modulate appetite include:

a) *Cephalic Phase Stimulation*. In this respect, some studies maintain the hypothesis that failure to stimulate the cephalic phase response can increase the risk of obesity, conversely others claim that stimulation of cephalic phase responses, from ingesting of simply being exposed to sweet foods, can be problematic because it stimulates both appetite and food intake. Another proposed mechanism could be mediated by the direct effect of non-caloric sweeteners on insulin secretion and glucose metabolism[13].

b) *Nutritional and osmotic effects*. It is known that the stomach produces appetite signals, mainly based on the volume it can or cannot cover, whereas in contrast, the bowel is more sensitive to signs of the presence of nutrients, even though this hypothesis does not appear to be fulfilled as strictly as the presence of osmo-receptors, at an intestinal level, and chemoreceptors, at a gastric level, imply. It has been proven that with gastric distension, whether it's due to the presence of nutrients or for another reason (gastric balloon), the feeling of fullness increases. Drinks which contain caloric sweeteners have more energy in terms of osmotic load which can be the same or even less than the load produced by non-caloric sweeteners, which means to say that with the same osmolarity the calorie content of non-caloric sweeteners is less; therefore gastric emptying doesn't just depend on osmolarity (chemoreceptors/osmoreceptors). However, caloric sweeteners cause slower emptying regardless of the osmotic effects.

Activation of signals both in the gut and in the stomach, from the presence of nutrients, have a synergistic effect on satiety. It has been hypothesized that drinks containing non-caloric sweeteners can weaken this effect present in those which contain nutritive sweeteners, even though no clear data really exists on this matter[13].

c) *Responses of gastrointestinal peptides*. Each macronutrient stimulates the release of peptides in the digestive tract with varying degrees of effectiveness. so, it has been proven that carbohydrates stimulate the secretion of GLP-1, which plays a significant role both as a satiety and incretin factor.

It is thought that non-caloric sweeteners don't permit such a release of peptides and therefore, in theory, this would mean a lesser feeling of satiety and would cause an increase in energy intake.

Some more recent evidence shows that there are receptors, with properties similar to the sweet receptors located on the tongue, in the gastrointestinal tract that stimulate the release of GLP-1, which could give non-caloric sweeteners a role in regulating these incretin systems.

d) *Palatability*. Another of the major benefits of using non-caloric sweeteners, as part of the diet, is to improve the organoleptic properties of the food in question, thus enabling improved acceptance both of the foods themselves and reduced calorie meals in which any food of this type is used, compared with its original higher calorie version and which may contain sugar as such, which undoubtedly contributes to optimal organoleptic properties. This might be a huge advantage in overweight, obese or diabetic patients with a view to improving adherence to treatment regimes and changes in nutritional habits. The hypothesis is whether the degree of food palatability affects appetite sensation, but following numerous studies there is still no conclusive evidence on this matter.

e) *Changes in gut microbiota*. It has been proven that changes in bacterial populations, which make up the gut microbiota, can contribute to the low-grade chronic inflammatory process which is observed in some obese patients and which seems to promote weight gain at the expense of fat mass, as well as actively contributing to the development of the comorbidities typically associated with obesity, such as insulin resistance[14].

Aspartame releases a methanol molecule, which is metabolised into a formaldehyde molecule, a highly reactive substance which is classified as carcinogenic. However, the amounts of these dangerous substances that are ingested, are usually well below the levels of risk. Therefore, it is not unusual for very small amounts of sweeteners to alter intestinal flora, as they act as the first line of defence in the gut and are therefore in direct contact with the sweetener and its metabolic compounds. During low-calorie diets for weight control the use of sweeteners like aspartame can change the optimal functioning of gut microbiota[15].

f) *Overcompensation*. Studies show that saving/withdrawing energy by substituting foods with non-caloric sweeteners could subsequently lead to over-compensation of food intake later on, which may even exceed the energy deficit induced by the sweetener and therefore cause a positive energy balance.

g) *Loss of signal fidelity*. Certain sensory properties of food influence the metabolic response required for each product. So, if the sensory input of sweetness by non-caloric sweeteners leads to an inaccurate or inconsistent prediction, energy regulation could be affected and lead to a positive energy balance due to excessive intake caused by these signals.

h) *Activation of reward systems*. It's possible that the improved palatability of sweetened products could play a role in stimulating food reward.

i) *Learning through the positive reinforcement of sweet flavours*. It refers to the possibility that repeated exposure to non-caloric sweetener can perpetuate a preference for sweet products in the diet, including those sweetened with caloric sweeteners[10].

Sweeteners and their effect on body weight

For many years, weight management has been one of the main reasons for the extensive use of sweeteners as part of a regular diet. However, from 1986 onwards doubts surfaced over the possible effects on weight gain, according to the results of surveys conducted by the American Cancer Society (ACS)[13].

Furthermore, in many instances an increase in use has not been accompanied by a reduction in nutritive sweeteners, which they are intended to replace with the aim of reducing calorie intake, consequently intake remained unchanged. The extent to which foods are chosen where nutritive sweeteners have been replaced by other non-caloric sweeteners should also not be overlooked, as, in the majority of cases, this leads to an increase in fat and protein content which may be trying to compensate for the calorie deficit caused by the food containing non-caloric sweeteners.

Changes in appetite regulation are responsible for changes in energy intake and therefore managing body weight. So, all the mechanisms of appetite regulation mentioned in the previous section may be involved in weight gain.

Changes in neural response mechanisms have been proposed as a possible explanation for the weight gain associated with sweetener use. It is known that the act of eating and the satisfaction derived from it, is the result of sensory stimulation from foods after ingestion. In humans, when a food is swallowed the taste, which is detected by receptors found in the oral cavity, ascends via the thalamus and reaches the area of the anterior insula frontal operculum as well as the frontal orbital cortex. Similarly, the amigdalae also make connections, via the taste pathway, at every level. Last but not least, the role played by the mesolimbic dopaminergic system is discussed, as it is responsible for recognising the stimuli and the pleasure/satisfaction sensation following the ingestion of food.

Following studies on rats, it has been demonstrated that the hypothalamus mediates the postprandial effect on the food reward system, given its different functions in the secretion of various peptides which regulate energy, osmotic equilibrium and behaviour in the presence of food. We increasingly have more evidence which shows that artificial sweeteners don't activate the food reward cascade in the same way as natural sweeteners, as it appears that the lack of calories suppresses the post-ingestive component. Moreover, the gustatory branch activation mechanism also differs in each case.

The sweet taste of non-caloric sweeteners may boost the appetite and dependency on such flavours, and there is a high correlation between the repeated exposure to a flavour and the degree of preference for it. Research in this field, but on the reduction of fat and salt in the diet, showed how with reduced exposure, the group's preference for these products diminished, so a possible theory has been put forward that the presentation of unsweetened diets could be one of the keys to reducing sugar consumption and consequently reverse the obesity epidemic[16].

These aforementioned hypotheses which have already been brought to light in previous studies, are also reflected in the research carried out by the American Academy of Nutrition and Dietetics[3], where it was observed that the sweeter a product is, the higher the consumption of food or drink will be. For the test subjects, the effect on appetite, caused by the repeated exposure to sweeteners, is due to an interruption of the hormonal and neurobehavioral pathways responsible for controlling hunger and satiety.

With regard to the risks of cardiovascular disease associated with weight gain, the prospective observational studies which exist to date only allow the identification of casual associations, but they are not in any way determinants; in many cases reverse causality is very plausible for some of the significant associations observed[10].

Sweeteners and diabetes

The potential benefits attributed to non-nutritive sweeteners for diabetics are the reduction in calories and carbohydrates which improve weight control and blood sugar respectively.

Various studies have shown that the use of non-caloric sweeteners does not seem to affect blood sugar or plasma lipid levels in adults with diabetes; it has not been researched sufficiently in children17. Diabetics should take into account total carbohydrate intake in order to improve blood sugar control. It has been suggested that blood sugar and weight control can be improved by using non-caloric sweeteners better than with sugary foods.

Two transporters are involved in the control of glucose absorption through the gut wall, the sodium-glucose linked transporter (SGLT1) which has an active role as a transporter in the apical membrane, and the facilitated glucose transporter (GLUT2), present both in the basolateral and apical membrane. The cells responsible for their absorption are enterocytes. Sugars as well as low calorie sweeteners that may be present in the diet, increase SGLT1 mRNA, protein expression and the absorption capacity for glucose; furthermore, given the relationship between SGLT1 activity and the insertion of GLUT2 in the apical membrane, T1R3 stimulation (sweet taste receptor subunit), also promotes a greater insertion of GLUT2.

Enteroendocrine cells communicate with enterocytes by producing signals which are detected by the latter, increasing SGLT1 expression. These incretin signals include glucose-dependent insulinotropic polypeptides (GIP) and GLP-1, which have numerous effects on glucose metabolism, including the stimulation of insulin release, inhibition of glucagon secretion, reduced gastric emptying and an increase in the feeling of fullness. As for the other mechanisms that have been described, the date available comes from in vitro and other short term studies, as well as studies on animals, which implies significant limitations on the extrapolation of results to human studies[18].

The effects of specific sweeteners on postprandial glycaemia, insulin and blood lipids have also been studied. As a result, following the comparison of a diet rich in sucrose versus another which, in contrast, contains non-caloric sweeteners, there is a significant increase in both postprandial blood glucose and postprandial insulinaemia, and blood lipid levels in a slightly overweight but healthy population, for the group with a diet rich in sucrose[19].

If we look at the latest American Diabetes Association (ADA 2013) recommendations20, with a B level of evidence, it states that in the case of type II Diabetes Mellitus, patients should limit their consumption of sugary drinks without specifying the appropriate number. There are no specific ADA recommendations that include other sources of sweeteners, apart from in soft drinks, where decreased consumption is recommended. We can also add that there are no recommendations on limiting the use of other sources of sweeteners.

Information on sweetener use should be transmitted clearly during diabetic education sessions. Accurate proven information, based on the best scientific evidence available, is necessary, so that relevant decisions and recommendations concerning their consumption can be made. In this respect, it is essential to disprove the myths which frequently surrounds this issue as well as combat the disinformation/misinformation that we come across on the internet and in the media on a daily basis. Research on non-caloric sweeteners gathered by regulatory agencies (FDA) contributes to their safe use and their potential benefits in controlling blood sugar.

Sweeteners and tooth decay

A cavity is formed by the localised destruction of hard dental tissue by acidic material which comes from the fermentation processes carried out by certain pathogenic bacteria, cariogenic bacteria, from fermentable carbohydrates present in the diet. Other factors which contribute to the development of tooth decay are microbiological changes in bacterial flora, saliva composition and its pH buffering capacity, the type of sugary foods consumed and the frequency of their consumption, and the quality and regularity of oral hygiene. Among the large group of sweeteners and according to the health claims that they help prevent cavities, the sugar alcohols erythritol, D-tagatose, sucralose, and isomaltulose, have been approved for consumption[5].

A global view of sweetener use: SWOT Analysis

Once all the matters relating to the general aspects of sweetener use and their possible metabolic effects on the body have been addressed, an overview of their use will be given, in accordance with the SWOT analysis system (Fig. 3).

Strengths

- Growing interest and the discovery of nutraceutical products with sweetening properties.
- The supposed beneficial effects of sweetener use as a whole, on metabolism, in different diseases (Obesity, diabetes, tooth decay) carving out a niche for them in the food industry.
- Non-caloric sweeteners provide sweetness without the extra calories or in the worst case scenarios, never as high as sugar.
- Large potential market demand associating them with a more balanced diet, although according to international organisation recommendations such as the FAO/WHO, the consumption of simple carbohydrates (sugars) below 10% of the total

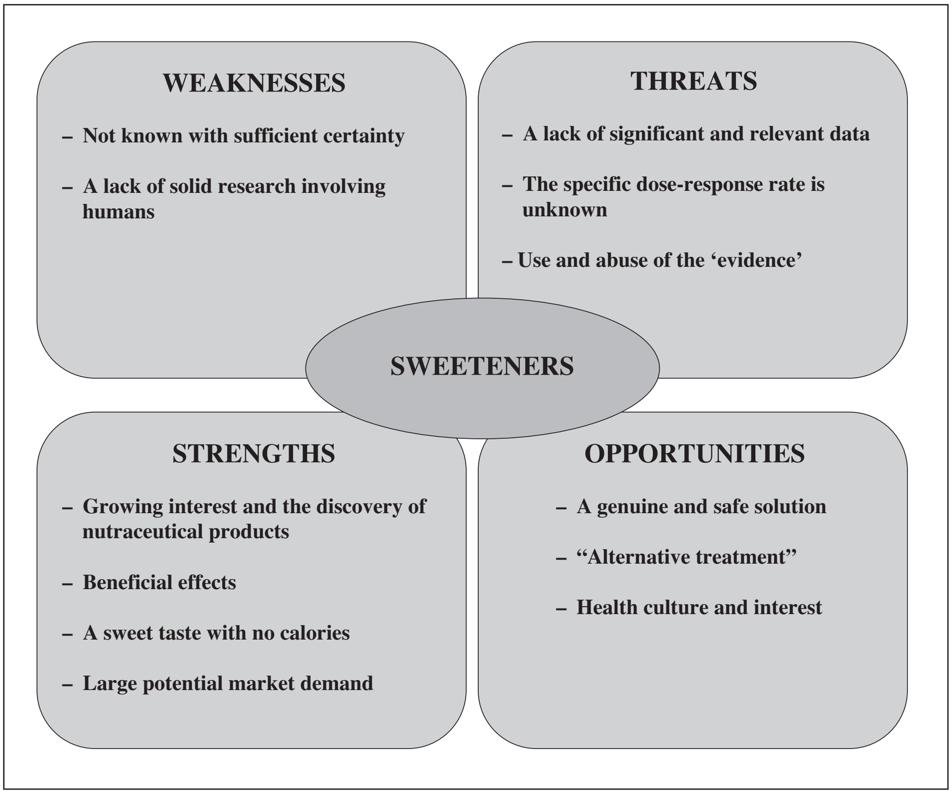

Fig. 3.—SWOT analysis on the use of sweeteners.

dietary energy is acceptable as part of a healthy balanced diet.
– They appear to help limit refined sugar consumption in the diet

Weaknesses

– The general population, including many health professionals, often lack correct knowledge on the particular characteristics of the different sweeteners available in the market, such as advising on and/or choosing a particular sweetener based on its properties.
– Even though the production-demand binomial is gradually becoming more evident in society, in the search for 'possible solutions' for improving health, there is actually a real lack of sound research on humans which confirms their potential benefits.

Opportunities

– They could eventually be a genuine and safe solution, taking into account an increase in chronic illnesses in society today (diabetes, obesity).
– They could become an 'alternative treatment', for the prevention and favourable evolution/ management of certain illnesses.
– As the years go by, the culture and interest in looking after the body and achieving optimum health grows. Included here are any criteria which could be a way of achieving this (i.e.: physical activity, specific diets, consumption of diet foods).

Threats

– A lack of significant and relevant scientific data.
– The specific dose-response rate, which clarifies the metabolic effects of their use, is unknown.
– Derived from previous ideas, use and abuse of 'evidence' to date in order to recommend for use.

Recommendations

Considering the existing disputes over their potential benefits and the importance and cost to public health at the moment because of the high incidence of chronic diseases (in particular obesity and its long-term consequences), sweeteners could be an alternative strategy in dietary treatment, as well as both a primary and secondary preventative measure in the treatment of obesity and its associated conditions. However, and despite the need for higher quality clinical research and while this takes places, once again moderation and the false myth of a 'miracle food' should not be consigned to healthy structured eating patterns which tend towards calorie balance through a variety of natural healthy foods, that are adapted to our customs without forgetting to combine this with a healthy active lifestyle.

We need to avoid indiscriminate use of them[13], as their potential interest as a tool for preventing excess weight or diabetes, even in the healthy population who want to take care of their health, has not been proven with evidence that supports their beneficial effects over the alternative standard caloric sweeteners[2].

In any case, the American Academy of Nutrition and Dietetics' position that any individual can use them safely is true, but only if they form part of a diet based on dietary recommendations and reference intakes for the general population, without forgetting, on the other hand, personal preferences and health objectives. Irrespective of non-caloric sweetener use in the diet, it is essential to control the total energy intake and increase the degree of physical activity in order to maintain body weight.

Recommendations from scientific societies (ADA, AHA) confirm that sugar alcohols and non-nutritive sweeteners are safe if daily dietary intake is within the levels established by the regulatory agencies (FDA, AESAN)[5].

Conclusions

So far, the existing evidence on the benefits of using non-caloric sweeteners as part of the population's regular diet and nutrition, is lacking in long-term results which are of significant scientific relevance, and the majority are epidemiological studies.

There are plenty of results on their effects and benefits from studies on animals, but not so many on humans due to bias and limitations on the interpretation and extrapolation of population data. On the other hand, it is necessary to determine the exact dose-response rate, which explains the metabolic effects of their use.

Likewise, and even though sugar consumption can be limited in patients with metabolic disorders, there is no evidence that recommendations on the use of sweeteners has been sufficiently scientifically proven to recommend the supposed long-term benefits of their use.

In 2009 the AHA concluded that limiting added sugars is a core strategy for maintaining optimum nutrition and a healthy weight. Likewise and for its part, the ADA has included monitoring carbohydrate consumption (which includes limiting added sugars) in their clinical practice recommendations, as a key strategy[10].

Finally, it should be noted that all non-caloric sweeteners approved for use are deemed to be safe, within permitted usage levels. Intake estimates are difficult to assess, if you also take into consideration that, in the majority of cases, food products contain a mixture of them which makes them even more difficult to calculate. It is essential that future studies on their consumption include a sufficient number of subjects, consumers in the 95th percentile, and even other groups that may have an above average intake (e.g. diabetics) or groups with particular issues (pregnant women or children).

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