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Review

The safety and regulatory process for low calorie sweeteners in the United States

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HIGHLIGHTS

- An outline of the current regulatory position of high potency sweeteners in the United States is provided.
- An evaluation of the safety and regulatory requirements was undertaken.
- The food additives Generally Recognized as Safe process were contrasted and compared.

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ABSTRACT

Low calorie sweeteners are some of the most thoroughly tested and evaluated of all food additives. Products including aspartame and saccharin, have undergone several rounds of risk assessment by the United States Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), in relation to a number of potential safety concerns, including carcinogenicity and more recently, effects on body weight gain, glycemic control and effects on the gut microbiome. The majority of the modern day sweeteners; acesulfame K, advantame, aspartame, neotame and sucralose have been approved in the United States through the food additive process, whereas the most recent sweetener approvals for steviol glycosides and lo han guo have occurred through the Generally Recognized as Safe (GRAS) system, based on scientific procedures. While the regulatory process and review time of these two types of sweetener evaluations by the FDA differ, the same level of scientific evidence is required to support safety, so as to ensure a reasonable certainty of no harm.

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1. Introduction

While the characteristics of low calorie sweeteners have been known for more than a century following the discovery of saccharin by Dr. Constantine Fahlberg in 1879 [1–4], it is only recently that their effectiveness in terms of calorie reduction, weight management and potential beneficial effects for patients with diseases such as Type II diabetes has been called into question [5–7]. This group of products have a high sweetness potency compared to sugar on a weight-for-weight basis. This results in only low amounts being required to be added to foods and beverages as a sugar substitute, thereby reducing the number of calories consumed, while still providing sweetness. It has long been assumed that the reduction in caloric intake in combination with changes in other lifestyle factors would provide both a weight management tool and a benefit for diabetics [8]. The sweetening intensities of these

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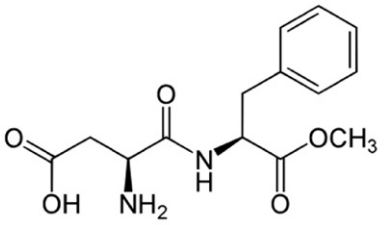
products range from 30 up to 20,000 times the potency of sugar for cyclamate and advantame (the latest United States (U.S.) Food and Drug Administration (FDA) approved sweetener), respectively. When blended together low calorie sweeteners can have synergetic qualities in terms of sweetness potency, sensory characteristics, and an increased shelf life, with the classic sweetener blends being saccharin and cyclamate (1:10 ratio) and aspartame and acesulfame K [9]. The sweetener of choice for many years was the cyclamate/saccharin combination. This was until concerns arose regarding the potential to cause bladder carcinogenicity within rodent toxicology studies, and the discovery that cyclamate was also metabolized to cyclohexylamine with toxic potential. Given this, the FDA chose to remove its Generally Recognized as Safe (GRAS) status in 1969 and to totally ban cyclamate in 1970 [10–12]. Even though the conduct of subsequent studies has proven that cyclamate is not a carcinogen, the ban on cyclamate remains in place in the U.S. today, although it is approved for use internationally with the exception of a few countries including Japan [13–15]. In contrast, in 1977 U.S. Congress placed a moratorium on a ban of the use of saccharin, while additional studies were conducted. The law also required that products containing saccharin contain a label warning that the "Use of this product may be hazardous to your health. This product contains saccharin which has been determined to cause cancer in laboratory animals". The saccharin warning was subsequently removed in December 2000 [16].

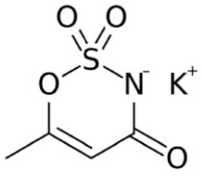
Although the members of this group of materials all impart sweetness, they show differences in properties such as potency, mouth feel, duration of sweetness, aftertaste and stability, and are all structurally different. Such differences thereby necessitate separate safety evaluations and regulatory reviews by the FDA and other global regulatory bodies such as the European Food Safety Authority (EFSA), Food Standards Australia New Zealand (FSANZ) and Health Canada (HC). It is, therefore, inappropriate to group these materials together from a safety perspective because they are handled differently once consumed from a metabolic and pharmacokinetic standpoint, even though they all act at the site of the sweet taste receptor [17]. The differences in the structures of the molecules are clearly outlined in Fig. 1.

2. U.S. regulatory processes

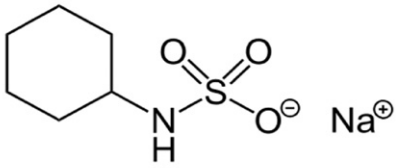
Low calorie sweeteners more than any other type of food additive, have engendered a great deal of controversy and debate over recent years, in relation to their increased usage and incorporation into many different dietetic food and beverage products. However, their usage in this manner would not have been possible without having first undergone a thorough safety evaluation by the FDA and other international regulatory authorities, prior to their approval for use in the food supply and listing in the Code of Federal Regulations. In the U.S., low calorie sweeteners are considered to be either food additives or GRAS ingredients. Currently those sweeteners that are approved food additives in the U.S. include acesulfame K, advantame, aspartame, neotame and sucralose, with the use of these products all permitted by and under conditions of a specific regulation. Saccharin on the other hand, was originally considered GRAS on the basis of its human use prior to 1958. However, the FDA withdrew its GRAS status following concerns regarding the potential to cause cancer in the bladder of rats provided high concentrations when fed over two generations and issued an interim food additive regulation limiting its use in 1977, which still holds today [18,19]. The low calorie sweeteners that are FDA listed GRAS ingredients include, steviol glycosides and lo han guo (monk fruit) and, in contrast, to those products approved through the food additive route, GRAS ingredients are permitted through either history of use and/or scientific procedures by qualified experts [20]. GRAS status based upon scientific procedures requires that the safety of the ingredient is supported by scientific studies, usually in the form of animal toxicity or human tolerance studies and that such an opinion would be endorsed by qualified experts.



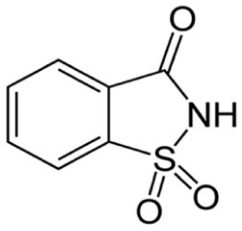
Aspartame
- 200x sweeter than sucrose
- FDA approved



Acesulfame K (Ace-K)
- 200x sweeter than sucrose
- FDA Approved



Cyclamate
- 30x sweeter than sucrose
- FDA banned



Saccharin
- 300x sweeter than sucrose
- Marketed in the U.S. as a sweetener for around 100 years

Fig. 1. Low calorie sweetener structures.

3. The food additive petition process

The regulatory route of choice for the majority of those permitted low calorie sweeteners has been *via* the food additive petition (FAP) process. Since this route has proved to be both a lengthy and costly exercise, companies are now looking to the GRAS procedure in the U.S. as a means of bringing their ingredients to the market place. The information required to complete a FAP, include both technical and safety related aspects; however, unlike GRAS substances, the scientific data is not required to be known to the scientific community at large. From a technical standpoint and pursuant to the provisions under section §171.1 of the Code of Federal Regulations, a food additive dossier is required to contain information regarding the identity of the food ingredient including its name, chemical identity, its composition, source and specifications. Detailed manufacturing methods are also required, as well as the provision of several product batch analyses and their accompanying certificates of analysis. Corroboration of the stability of the bulk ingredient and within a cross section of food matrices must also be provided, along with the analytical methods of identification for the sweetener and any potential impurities. It is also important to include evidence