Nonnutritive Sweeteners

By: Stephanie Puccinelli, Jason Tien, Calvin Wang, Joanna Wirkus, and Noel Zeng
University of California, Davis

Abstract

Various nonnutritive sweeteners, or calorie free sugar substitutes, have been used commonly in the US for over 50 years. However, their usage and development has not been without scrutiny. Today, consumers range from stanch supporters to abstaining skeptics. Despite extensive testing, their health related concerns adversely affects consumption. Our paper examines the Food and Drug Administration (FDA) approval process of nonnutritive sweeteners; it also reviews acesulfame K, neotame, sucralose, stevia, saccharin, and aspartame in detail. Each sweetener is described based on its discovery, regulatory history, and chemical composition. Food examples and organoleptic properties are examined, as well as metabolism, food safety, and controversy. Finally, we examine the consequences of long term consumption, and the food industry drivers, inputs, processes, and outputs that relate to zero calorie sweeteners.

Keywords: Acesulfame K, Neotame, Sucralose, Stevia, rebiana , Rebaudioside A, Saccharin, Aspartame, artificial sweeteners, nonnutritive sweeteners,

Introduction

People want to have their cake and eat it too, without gaining any weight. Artificial sweeteners are proof of a cultural desire to enjoy sweetness (which we are all evolutionarily hardwired to do) yet avoid the inadvertent consequences that come along with consuming too many empty calories. Some studies suggest that, physiologically speaking, our bodies are better equipped to balance the consumption of excess calories from food. When extra calories come from beverages, hunger and satiety hormones are not as effective as they are with solid food. From an evolutionary perspective, the majority of early humans drank nothing but water and breast milk, so it's not surprising a novel caloric load could potentially have undesired results (Wolf, Bray, & Popkin, 2008).

Purified sugars are popular commodities, and added sugars are seen ubiquitously in processed foods. Manufacturing companies have taken advantage of the preservative properties of sugars, as well as the improved flavor and appreciation for sweetened products. An increase in obesity over the last 40 years has captured the attention of the nation. Naturally, the increase in sugar consumption (particularly in the form of sweetened beverages) has been blamed for contributing to increased calorie intake and overall weight gain in a subset of the population. Problematically, all stores sell bottled empty calories as sweetened drinks. Not to mention, advertisers have successfully attached an image and a sensation to a product that have left kids, adolescents, and adults equally at risk of falling into the consumer trap. Since these products have a real potential to increase energy intake and energy storage, it is clear why non-sugar sweeteners are so popular. Sweetness is a sensation that our brain always perceives as pleasurable so it's no surprise that non-sugar sweeteners had $9.2 billion dollars in worldwide market

share in 2010 ("Global Markets for Non-Sugar Sweeteners [Abstract]," 2011).

Naturally, one suggested solution to a nationwide public health crisis has been to partially or fully replace the sweetness people know and love with zero calorie alternatives. The Academy of Nutrition and Dietetics states that "… consumers can safely enjoy a range of nutritive sweeteners and nonnutritive sweeteners when consumed within an eating plan that is guided by by current federal nutrition recommendations..." (Fitch & Keim, 2012). The approval of the FDA leads consumers to assume absolute safety when considering consuming these food additives. The American Dental Association also touts the non-cariogenic properties of a variety of non-sugar sweeteners ("Current Policies 1954-2008," 2009). While this argument is valid for chewing gum and toothpaste, soda's inherent acidity promotes tooth decay. According to the American Diabetes Association, nonnutritive sweeteners are also an important component of managing diabetes, as they do not elicit an insulin response and can be used in an effort maintain stable blood sugar (ADA, "Artificial Sweeteners").

The food industry's search for tasty and sin-less sweetener may never end, but what are the consequences of tricking our taste buds and cheating our metabolism?

First, it is important to understand the process for FDA approval of nonnutritive sweeteners. Second, this paper explores acesulfame K, neotame, sucralose, stevia, saccharin, and aspartame in detail, considering discovery, regulatory history, chemical composition, organoleptic properties, examples of its use, food safety, and controversy. Next, the implications of long term use of nonnutritive sweeteners is considered. Lastly, the overall food system drivers including inputs, processes, and outputs as related to the use of artificial sweeteners are explored.

NEW ARTIFICIAL SWEETENER APPROVAL PROCESS

When deciding between different types of artificial sweeteners, consumers are typically limited

to the information provided by food labels, their personal preferences, or a combination of both. Their ability to assess the safety and health benefits associated with consuming a particular artificial sweetener is beyond their scope and knowledge. Consequently, the FDA has been entrusted with the responsibility of overseeing and regulating the safety of food ingredients, including the premarket safety assessments of new artificial sweeteners. The FDA regulates artificial sweeteners as food additives. Therefore, new artificial sweeteners undergo the same assessments and studies as any new food additives would undergo.

The 1958 Food Additive Amendment place new artificial sweeteners under strict pre-market safety evaluations to ensure that they are safe for their intended use prior to marketing. The only two exceptions to this approval process are if the proposed use of the artificial sweetener is a prior-sanctioned substance or Generally Regarded as Safe (GRAS) (FDA, 2011). To market a new artificial sweetener—that is either not considered a prior-sanctioned substance or GRAS—a manufacturer or other sponsor must first submit a petition to the FDA (FDA, 2011). The petitioner must include in their petition all relevant safety data—that which may or may not support its safety—about the new artificial sweetener. The information submitted includes data detailing the chemical identity of the substance, its purity, its environmental effects, and other technical specifications (Rulis & Levitt, 2008). But most importantly, the data must allow FDA scientists to measure the Estimated Daily Intake and determine the Acceptable Daily Intake (ADI) of the additive (Rulis & Levitt, 2008). The new artificial sweetener is then examined and evaluated by teams of scientists assembled by the FDA from within the Office of Food Additive Safety (OFAS). A typical review team consists of chemists, toxicologists, and "consumer safety officers" (CSOs). Once approved, the new artificial sweetener must be safe for everyone including children, teenagers, adults, the elderly, and pregnant/lactating women. Additionally,

the FDA will issue regulations specifying the type of foods in which it can be used, the maximum amounts to be used and how it should be identified on food labels.

Currently, the FDA has approved the following six artificial sweeteners for use in foods and beverages: saccharin, acesulfame, neotame, sucralose, aspartame, and stevia. Cyclamate, which was once approved by FDA, was banned in the U.S. in 1970. Long-term lab tests performed with rats had proved it carcinogenic when mixed with saccharin (Misner, Curtis & Whitm er, 2008). However, it is still used in many parts of the world, especially Europe.

Acesulfame K

Acesulfame potassium, or generically known as acesulfame K, is widely used in foods, beverages, cosmetics, and pharmaceutical formulations. It was first approved by the FDA in 1988 for specific use in a variety of dry products such as a tabletop sweetener. In 1998, it was approved for use in non-alcoholic beverages. Finally, in December 2003, it was approved for general use in food except in meat and poultry (Misner, Curtis & Whitm er, 2008). Presently, it is marketed under the trade names Sunnet ® or Sweet One ®.

Acesulfame K was first developed by Karl Clauss and Herald Jensen at Hoechst AG after an accidental discovery of a similar compound belonging to the class of dihydro-oxathiazinone dioxides. Of the many compounds synthesized from this new class of substances, *6-Methyl-1,2,3-oxathiazin-4(3H)-one-2,2-dioxide* demonstrated better sensory properties than the other compounds. Studies involving the synthesis of several salts for *6-Methyl-1,2,3-oxathiazin-4(3H)-one-2,2-dioxide* showed that the potassium salt of this compound was most easily manufactured (Mitchell, 2006). Consequently, the potassium salt of *6-Methyl-1,2,3-oxathiazin-4(3H)-one-2,2-dioxide*, otherwise known as acesulfame K, was selected

as a marketable artificial sweetener.

The potassium salt of *6-Methyl-1,2,3-oxathiazin-4(3H)-one-2,2-dioxide* is synthesized from acetoacetic acid *tert*-butyl ester and fluorosulfonyl isocyanate to form flurosulfonyl acetoacetic acid amide that cyclises in the presence of potassium hydroxide to form the oxathiazinone dioxide ring system. The strong acidity of oxathiazinone dioxide ring system results in potassium salt formation (Rowe, 2005). An alternative process to synthesizing acesulfame K is based on diketene and amidosulfonic acid which reacts in the presence of dehydrating agents and then is neutralized with potassium hydroxide to form potassium salt. The latter process involves starting materials that are easier to handle than the former.

Acesulfame K appears as a colorless to white-colored, crystalline powder and has a sweetness intensity of about 200 times greater than sucrose. When consumed in small amounts and combined with other sweeteners, acesulfame K has no lingering, bitter aftertaste. As a matter of fact, it has synergistic effects when combined with aspartame, sodium cyclamate, and sucralose. A ternary blend of acesulfame K with aspartame and sodium cyclamate may enhance the sweetness by as high as 90% (Mitchell, 2006). Blends of acesulfame K with other components not only synergistically enhance sweetness, but can mask the bitter aftertaste of other sweeteners. Acesulfame K is relatively heat stable and freely soluble in water. It can also withstand acidic and basic conditions thereby allowing it to be used in baking and products with long-shelf life. Furthermore, sterilization and pasteurization does not affect or alter the sweetness of acesulfame K (Rowe, 2005).

Physiologically, acesulfame K is rapidly absorbed and excreted in the urine unchanged. In other words, it is not metabolized by the body. Its non-caloric properties make it suitable for low-calorie food products and diabetics. Generally, this artificial sweetener is relatively nontoxic and non-irritant. But

there is controversy surrounding its carcinogenicity. Critics have claimed that the testing carried out for Hoechst in the 1970s were inadequately designed and executed and therefore lacked adequate evidence to disprove acesulfame K as a potential carcinogen (Karstadt, 2006). Similarly, others have argued that the results of some animal experiments suggested acesulfame K increases the risk of cancer. Another controversial concern involves the need for further studies to determine whether the acetoacetamide formed in beverages during storage is hazardous to consumers. However, all of these claims have been dismissed by the FDA (Kroger, Meister, & Kava, 2006).

Neotame

After the great success of aspartame, the Monsanto Corporation was motivated to create a new product that would be safe for all individuals to consume especially those with the genetic disorder phenylketonuria (Newton, 2009). In the 1990's, Monsanto researchers Jean-Marie Tinti and Claude Nofre, embarked on a mission to produce a safer and less costly product, as well as one with increased stability and potency (Newton, 2009). The efforts of the team led to the discovery of the nonnutritive sweetener neotame which was later approved by the FDA in 2002 (Newton, 2009).

The scientific name for neotame is *N-(N (3,3 dimethyl butyl-L a aspartyl –L phenylalanine 1- methyl ester)* (Newton, 2009). It is a derivative of aspartame and shares the same dipeptide containing aspartic acid and phenylalanine, but it also has a dimethyl-butyl- aldehyde group protecting the dipeptide from peptidases (The NutraSweet Company, 2008). This artificial sweetener also has higher heat tolerance, pH stability, and increased water solubility—making it functional in a variety of food systems and cooking applications such as baking (Nofre & Tinti, 1999). The intensely sweet neotame is 7,000-13,000 times sweeter than sucrose and provides zero calories. (Newton, 2009) It offers a clean and sweet flavor profile with no bitter aftertaste which is often associated with many

nonnutritive sweeteners (Facts About Neotame, 2008). Because of this, neotame can be used as the sole sweetening agent in a product or can be used synergistically as well. Because of its high potency, low levels of neotame are needed to sweeten products (Facts About Neotame, 2008).

According to researchers, neotame is readily metabolized by the body without any bioaccumulation (Nofre & Tinti, 1999). The methyl esters of the molecule are subject to hydrolysis by esterases within the body while the peptide bond between aspartic acid and phenylalanine remains intact (Facts About Neotame, 2008). Methyl esters are de-esterified by esterases throughout the body producing small amounts of methanol (Facts About Neotame, 2008). The remaining dimethyl-butyl moiety inhibits peptidases in the body from degrading the dipeptide in which no free phenylalanine is produced (The NutraSweet Company, 2008). It is estimated that nearly half is absorbed and excreted in the urine while the remaining unabsorbed material is excreted in the feces (Nofre & Tinti, 1999). Bacteria in the mouth are unable to metabolize neotame and therefore makes it a noncariogenic artificial sweetener (Nofre & Tinti, 1999).

Neotame has been the focus of 113 human and animal studies that confirms it is a safe food additive (The NutraSweet Company, 2008). It has been approved by the FDA and requires no special warning label that it contains phenylalanine, unlike its predecessor aspartame (The NutraSweet Company, 2008). It has been accepted by many health and food organizations such as The Academy of Nutrition and Dietetics and also the American Diabetes Association (American Dietetic Association, 2004). Neotame is used in a variety of products worldwide, but is not found in food products on the U.S. market (Facts About Neotame, 2008).

Sucralose

Despite the release of previous artificial sweeteners, sugar, in the mid-to-late 1970's, was an

abundant and relatively cheap commodity around the world. Compared to its artificial replacements, sucrose provided little profit for its producers (Newton, 2009). The British sugar company Tate & Lyle was looking to increase its profits in hopes of finding innovative ways to use the sugar molecule. Their ideas included chemicals, detergents and plastics (Newton, 2009). The company's ultimate goal was to increase the demand for sucrose, making it once again a profitable commodity. In 1978, Tate & Lyle bestowed upon Professor Les Hough of University at London's Queen Elizabeth's College the task of finding new utilizations for the table sugar molecule (Newton, 2009). While in the lab, Hough directed one of his graduate students to start testing the molecules but instead he started tasting them (Newton, 2009). The chlorinated sucrose molecule was indeed intensely sweet and became what is known today as sucralose. The FDA approved sucralose as a safe food additive to be used as a general purpose sweetener in 1999 (Grotz & Munro, An Overview of the Safety of Sucralose, 2009).

The systematic name for sucralose is *1,6 dichloro-1,6-dideoxy-B-fructofuranosyl-4-chloro-4-deoxy-a-D-galactopyranoside* (Nabors, 2012). It is composed of the disaccharide sucrose as well as specifically chlorinated carbons, replacing the naturally occurring hydroxyl groups. According to scientists, the glycosidic bond between the fructo-furanoside and galacto-pyranoside is highly resistant to enzymatic and acid hydrolysis and also is highly tolerant of heat making it applicable to various food systems (Nabors, 2012).

Like many non-nutritive sweeteners, sucralose also possesses an intensely sweet taste. It is 600 times sweeter than sucrose and contributes no calories. But unlike many of its predecessors, sucralose lacks the bitter aftertaste and is said to have a "clean" and sweet flavor profile similar to sugar (Nabors, 2012). Because of its high stability, sucralose can be used in a wide variety of foods ranging from cakes, cookies, and candies to dairy products and sweetened beverages.

Studies done in part of the FDA have indicated that sucralose is not readily metabolized by the body and therefore most of the chemical is excreted in the urine and feces. Other researchers estimate that 85% is absorbed in the intestinal lumen and is excreted in the feces making nearly 15% of sucralose absorbed and excreted via the urine, while 2-3% of the absorbed material undergoes glucuronidation which specifically leaves the body in the urine (Grotz & Munro, An Overview of the Safety of Sucralose, 2009).

Sucralose has been the subject of over nearly 110 rigorous human and animal studies making it one of the most tested food additives in the world (Nabors, 2012). It has been widely accepted by the FDA and The Academy of Dietetics and Nutrition as safe sugar alternatives (American Dietetic Association, 2004). Even though here has been wide acceptance of sucralose from organizations around the world, skepticism of the artificial sweetener still remains by many. Rigorous testing has been performed providing individuals with empirical evidence but many question the validity of these results. In 2008, Duke University studied the effects sucralose in male rats and discovered a correlation with decreased intestinal bacteria as well as increased expression of specific proteins limiting the absorption of certain kinds of prescription drugs (Abou-Donia, El-Masry, Abdel-Rahman, McLendon, & Schiffman, 2008). Many research teams who had established sucralose as risk- free prior to the Duke study, fired back at the university's findings claiming the experiment was poorly executed and disregarded their results (Browning, New Salvo in Splenda Skirmish, 2008).

Not only is there controversial debate surrounding the safety and use of sucralose, but sucralose has also been the subject of marketing scandal. In 1999, McNeil Nutrtitionals introduced sucralose on the market as Splenda ® which quickly gained popularity by consumers. Its success had greatly affected the artificial sweetener industry and ultimately led to the decline in popularity of its competitors

(Browning, Makers of Artificial Sweeteners go to Court, 2007). In 2004, both Merisant (the owner of Equal ® (Aspartame)) and The Sugar Association sued McNeil Nutritionals for false advertising when McNeil Nutritionals took advantage of the chemical structure of sucralose. Merisant and The Sugar Association believed that Splenda's slogan "it's made from sugar, so it tastes like sugar" misled consumers by giving them the false notion that Splenda® was a more natural and healthy option among the other alternatives available on the market (Browning, Makers of Artificial Sweeteners go to Court, 2007). Today, Splenda ® products no longer carry their infamous slogan that may have once misinformed the public on sucralose**.**

Stevia

The stevia leaves' sweetness has been utilized for medicinal purposes by indigenous people in South America for thousands of years. Today, it is commercially cultivated in Taiwan, Paraguay, South Korea, China and Brazil as well as many other countries around the world. Stevia is a very popular alternative sweetener worldwide, especially in Japan (Mitchell, 2006).

It was discovered by the western world in the late 1800's and the sweet compounds were isolated in the 1930's, this resulted in stevia being used in the US during the 1980's. Despite it's long history of use around the world, stevia was banned by the United States FDA in 1991 (Winter, 2009). Under the Dietary Supplement Health and Education Act of 1994, stevia extracts were permitted to be sold as a dietary supplement intended to be taken internally but were not permitted to be sold as a sweetener or food additive. Whole leaf stevia extracts are still not considered GRAS by the FDA ("Is Stevia an 'FDA approved' sweetener?," 2012). In 2008, the FDA approved rebaudioside A extract to be used as a food additive and sweetener and has granted GRAS status to the single isomer extract (Tarantino, 2008). This change in the market has led to the development of plant breeding technologies

to create varieties that produce high levels of the Rebaudioside A isomer (Mitchell, 2006).

The leaves of the *Stevia Rebaudiana* plant are cultivated, harvested, steeped in water for aqueous extraction, followed by extraction with a polar solvent. The product is then decolorized, purified, and crystallized (Mitchell, 2006). While stevia is a natural extract, it is highly processed. The main, sweet, isolated molecules that result from this process are called steviol glycosides. The most common and most studied isomers are stevioside and its analogue rebaudioside A (other analogues exist but are not studied or used extensively). The structure common structure in these analogues is the aglycone, steviol. Varying numbers of carbohydrate moieties are linked to the steviol backbone resulting in a variety of analogues. For example, stevioside (the most common isomer) has a disaccharide of two (1,2) B D-glucose moieties linked to the steviol on one side, and a beta linked glucose on the other. The other analogue of particular interest as a non sucrose sweetener, rebaudioside A, has a B D-glucose trisaccharide and a beta linked glucose attached to the steviol backbone. All the various steviol glycosides have different relative sweetness. Stevioside is 300 times sweeter than sucrose, while rebaudioside A is 250-450 times sweeter than sucrose. The polarity of the molecule influences the perceived sweetness and the molecule with higher polarity stimulates sweetness receptors more intensely. The stevioside molecule has a clear bitter after taste. Rebaudioside A is superior in flavor profile**.**

Since 2008, commercial products containing stevia extracts have taken the market by storm. True-via ® is a common commercially available preparation of erythritol (a zero calorie sugar alcohol), stevia rebiana (rebaudioside A) extract, and some natural flavors. ("Truvia", 2013) It is available as a tabletop sweetener but is also used in many commercial products including Vitamin Water Zero ®, Sobe ®, Odwalla ®, Hansen's ®, Blue Sky ® energy drinks and sodas, Crystal Light-Pure ®, and

other products including ice cream, yogurt and granola bars. Not all stevia containing products use Truevia ® and other popular commercial preparations include PureVia ®. Other examples of products containing stevia extracts include toothpaste, chocolate, teas, candy, and sodas.

Stevia extracts including stevioside and rebaudioside A are stable to heat and in acidic conditions. (Mitchell, 2006) They are appropriate for use in baking and carbonated beverages with citric or phosphoric acid. Products using stevia extracts can tout their natural, yet sugar free sweetener source, tapping into a market of health conscious individuals who may have previously been skeptical of artificial sweeteners.

Stevia extracts are not metabolized by humans but bacteria in the gut are able to cleave the glucose molecules off and use them for energy. (Gardana et al., 2003) Some of the steviol backbone is then excreted in the feces. The majority of the steviol backbone is absorbed and conjugated to form a glucuronide (Wheeler et al., 2008). This molecule is then excreted in the urine. Studies show that stevioside and rebaudioside A are metabolized at different rates, suggesting that toxicity studies should be conducted on each isomer individually. (Kobylewski, 2008). Risks researchers aim to understand when testing a possible food additive include the possibility of genotoxicity. The results from various studies are mixed. While many studies show no negative results, isolated studies done on animals and bacterial samples do show DNA breakage that occurs in the presence of stevia extracts of their metabolites. Therefore, stevia compounds and their metabolites require more careful controlled research studies in order to understand possible risks associated with its use.

Stevia sweeteners have had a controversial regulatory history. In 1999, stevia was determined to be unsuitable for use as a sweeter when reviewed by the JEFCA (Joint FAO/WHO Expert Committee on Food Additives) and Scientific Committee for Food of the European Union (Mitchell,

2006). This decision was made based on the limited amount of scientific evidence available at that time. In 2004, JECFA set a tentative ADI of 2 mg/kg of body weight for stevia extracts, provided that more studies be conducted by 2007 for risk assessment. Recently, JECFA claimed that several common stevia extracts are not genotoxic and are safe for use. ("Summary and conclusions of the sixty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)," 2008)

Saccharin

Saccharin is the oldest and the first commercially developed non-caloric sweetener used for consumer consumption. Also known as o-benzoic sulfimide, saccharin was first discovered in 1879 by Constantine Fahlberg of Harvard University while working with the coal tar derivative, toluene (Ophardt, 2003). Around this time, there were many contributing pressures that sparked the quick and continued popularity of this sugar replacement. The two World Wars, which led to sugar rationing in Europe and the United States, as well as society's sudden interest in a slimmer body image were two significant factors. Therefore, society desperately looked for sugar replacements in their everyday diets (Conis, 2010). Once manufactures and consumers realized saccharin could act as a sugar replacer by sweetening foods and beverages without contributing any calories or glucose, there was widespread popularity for this product. Therefore, after its discovery as a potential sugar replacement, saccharin began to be commercially developed by John F. Queeny by his company, Monsanto Chemical Company (Mitchell, 2008). By 1976, the saccharin business had already become a $2 billion dollar industry with 7 million pounds produced for domestic consumption (Pena, 2010).

Saccharin has a $C_7H_5NO_3S$ chemical composition and is obtained by the oxidation of o-methyl-benzenesulfonamide, which originates through material acquired from the chlorosulfonation of toluene with chlorosulfonic acid (Mitchell, 2006). Due to its age and extensive research, there have been

two discovered methods for the synthesis of saccharin. The original Fahlberg-Remsen process is nowadays considered unfavorable because the chlorosulfonation reaction that is required often results in ortho- and para-substitution products. A new modern process developed in the 1950s invented by Senn and Schlaudecker revolved around utilizing the common grape flavorant methyl anthranilate as the starting material (Mitchell, 2006). This modern way of synthesis has been applied to avoid undesirable forms saccharin. Through X-ray experiments, Dr. Y. Okaya, a crystallographer at IBM, was able to determine that the basic structure of the molecule consists of two joined rings, one containing six atoms, and the other containing five. The five-sided ring was flat, and the six sided benzene ring was squashed (Science News-Letter 1965). Although the exact science for why saccharin produces a sweet taste sensation is still not fully understood, scientific knowledge of taste bud receptors on the tongue can provide an explanation. Saccharin's physical structure contains three areas that fit perfectly into a taste bud's receptor site. These three taste bud receptor sites are located in: 1. An area which contains available hydrogens to hydrogen bond onto oxygen from the sulfur group. 2. An area with a partially negative oxygen available to hydrogen bond to a partially positive hydrogen of an amine group. 3. An area perpendicular to sites one and two which can attract the non-polar part of the benzene on the saccharin molecule (Ophardt, 2003). These discovered areas make it possible for one to taste this artificial sweetener.

Saccharin's discovery and early popularity was partly due to history's timing but more importantly for what the job it does in filling its purpose. Saccharin is found in tabletop sweeteners such as Sweet n Low ® and Sugartwin ®. It can also be found in common products such as juices, instant beverages, chapstick, toothpaste, and many more. Saccharin's flavor profile can be assessed by the FPA(flavor profile analysis), which was developed by Arthur D. Little Company in the 1940s. The

panels composed of expert tasters that were trained to break down complex and multiple flavor attribute systems to rate their component intensities. Here, studies were able to discover saccharin's potency, which is hundreds sweeter than sucrose, and its bitter and metallic taste at certain concentrations (Mitchell, 2006). However, studies have found that two thirds of the human population is not susceptible to taste 6-n-prophythiouracil, which gives off bitter/metallic tastes. (Bartoshuk 1979) Due to saccharin's high potency, smaller doses are needed for saccharin to fulfill its duty, which lowers costs for companies. Besides lowered costs, saccharin is also very easy to work with in the lab. In acid form, saccharin has a pKa of 2.32, and is poorly soluble. However in acid form, it is extremely soluble (Mitchell, 2006). Saccharin is also soluble in warm water as well as in the presence of alkalines or their carbonates ("The British Medical Journal", 1887). Saccharin is a very stable product (Mitchell, 2006). In fact, loss of sweetness during food product lifetime or a degradation of product safety is not a significant concern for saccharin.

In the body, saccharin is generally slowly and incompletely absorbed in the small intestine. There is typically 56-87% of saccharin excreted in the urine, and 10-40% of saccharin excreted in the feces (Lethco and Wallace, 1975). At high doses on rats, saccharin concentrates only slightly in the organs of excretion, the kidney and bladder. Most is concentrated in the plasma (Lethco and Wallace, 1975). Saccharin is not metabolized in humans or rats and does not bind to the DNA of the bladder—meaning it is not a carcinogen (Mitchell, 2006). If there are no conflicts concerning the metabolism and absorption of saccharin in the body, what is all the worry about?

The answer lies in saccharin's potential increased risk of bladder cancer. Due to saccharin's long history and experimentation, there is extensive regulation and controversy with this artificial sweetener. Questions concerning saccharin safety started in the early 1900s when its popularity

skyrocketed. President Theodore Roosevelt, a heartfelt defender, stated "Anybody who says saccharin is injurious to health is an idiot" (Junod, 2003). In 1977, there was the first clinical study that showed a positive association between saccharin and bladder cancer in humans ("Saccharin and Cancer: Confounding Data, 1977). This led to the immediate ban of saccharin in the United States by the FDA (Bidwell 2005). This was met with outrage, as many Americans had become so dependent on this sugar replacer, especially diabetics. Therefore, Congress placed a moratorium on the ban and instead required all food containing saccharin to bear the following warning label: "*Use of this product may be hazardous to your health. This product contains saccharin, which has been determined to cause cancer in laboratory animals*." ("Medlineplus,"2009). This burst of outrage that even caused Congress to place a moratorium on the FDA's decision shows the significance saccharin had on the daily consumer's lives.

Aspartame

During 1975 to 1984, the consumption of artificial sweeteners by American consumers increased over one hundred and fifty percent. This was attributed to the accidental discovery of aspartame by chemist J. D. Schlatter, who at the time, was attempting to synthesize ulcer medication. J. D. Schlatter worked for a corporation called G. D. Searle and Company, which is better known today as Monsanto. Monsanto began to market aspartame under the name Nutrasweet ® in 1981 after the FDA approved it in 1980, and the success of aspartame has created a $1.1 billion dollar industry.

Aspartame's formal chemical name is *L-aspartyl-L-phenylalanine methyl ester*, which is comprised of two main groups: a phenylalanine and aspartic acid. The chemical synthesis of these two structures can be done either chemically or enzymatically. However, chemical synthesis will yield a higher percent of (L), or a more optically pure product (Mitchell, 2006). It is relatively stable at room

temperature, despite that aspartame cannot be used in baking as heat hydrolyzes the phenylalanine and aspartic acid, rendering it tasteless. There is also a risk of hydrolyzation at a pH of 4.2 or lower (Mitchell, 2006).

The phenomenal discovery of aspartame led to a profound effect on the food industry during the 1980's, and by 1985 there were 1,200 Nutrasweet ® containing products on grocery store shelves, most of them outselling their sucrose sweetened counterparts (Pena, 2010). The success of Nutrasweet ® is also partially attributed to its organoleptic properties; its predecessor, saccharin, contained a bitter aftertaste. Aspartame did not have this effect and offered 180-200 times the sweetness of sucrose (Mitchell, 2006). The sweetness profile for aspartame is similar to sucrose, however there have been reports of a longer onset time and a lingering sweetness taste which is modified by the addition of naringin or potassium aluminum sulfate (KAl(SO4)2) (Mitchell, 2006). The bitter aftertaste of saccharin was addressed by the addition of minimal amounts of sugar, only offering consumers a low calorie alternative; Aspartame contains no calories, thus pioneering the first zero calorie diet beverages. The increased consumption of Nutrasweet ® alarmed the scientific community,and this resulted in both the FDA in 1985 and the European Commission Scientific Committee on Food (SCF) launching investigations regarding its safety in 2002.

The approval of aspartame within the FDA is still shrouded in controversy even today, however their findings are consistent with the more recent SCF findings. The SCF concluded in 2002 that nullified previous findings linking aspartame to brain tumors in rats (JW Olney, 1996). The SCF released this statement, "To this end, consideration has been given to aspects of metabolism and toxicity as well as to clinical studies conducted to address the reported adverse effects of aspartame in healthy and potentially sensitive individuals, consideration has also been given to recent estimates of intake…the

Committee concluded that on the basis of review of all the data in animals and humans available to date; there is no evidence to suggest that there is a need to revise the outcome of the earlier risk assessment previously established for aspartame" (European Commission Scientific Committee on Food, 2002).

The SCF did address many concerns on the metabolism and breakdown of aspartame, including the risk associated with phenylketonuria (PKU). PKU interferes with the digestion of aspartame as it becomes divided into three parts in the intestinal lumen; these parts are phenylalanine, aspartate, and methanol. The phenylalanine and degrades down to tyrosine and eventually becomes fumarate, while the aspartate turns into oxaloacetate; both fumarate and oxaolacetate are consumed during metabolism. However creation of methanol from aspartame concerns health officials, as high methanol levels can alter receptors within the central nervous system (Stegink, 1987). However this is not their only concern, those diagnosed with phenylketonuria or PKU lack the enzyme to convert the phenylalanine to tyrosine. The buildup of phenylalanine within the body of a PKU patient can cause retardation and even irreversible brain damage.

Although it only contributes to 7% of today's expanding artificial sweetener industry, aspartame and Nutrasweet ® completely changed the course of food during the 1980s. Aspartame pioneered calorie free options for consumers without the bitter aftertaste, while offering 180-200 times the sweetness of sucrose; this resulted in Nutrasweet ® being a major success. The increased consumption of aspartame triggered an investigation into its chemical effects, and both the FDA and SCF have deemed aspartame safe for consumption.

Long Term Use

The long term use of artificial sweeteners questions not only the health concerns associated with its use, but also the effectiveness of its purpose: to help people lose weight. Experts have questioned the

effectiveness of calorie free sweeteners as both artificial sweetener consumption and obesity have skyrocketed within the last three decades. The increasing obesity epidemic undercuts the effectiveness of more recently discovered sweeteners such as stevia and neotame, as their long-term dose responsiveness has not been well documented. However, much information has surfaced about sweeteners that have been on the market for longer, such as aspartame, cyclamates and sucralose.

A study conducted at The San Antonio Heart Study examined 3,682 adults over the course of nine years (1979-1988) concluded with a positive correlation between the development of adipose and the consumption of diet beverages. “The use of artificial sweeteners may be indirectly related to weight gain. Sugar consumption induces a sense of satiety and in its absence fat and protein intake typically increase” (PJ Rogers, 1988). The examiners also concluded that users of artificial sweeteners might also have overcompensated for the caloric savings (Mattes, 1990). These claims have created an interest in the neurology and epidemiology in the response to sugar and sweetness, as evidence in our eating habits begin to be discovered. The subjects within the San Antonio Heart Study saw an average increase of 1.01kg/m^2 in the control over nine years while users of artificial sweeteners saw an average increase of 1.78kg/m^2. (Fowler SP, 2008). Theses studies conclude that users of artificial sweeteners may experience weight gain as evidence points to over compensation, altered eating habits and other epidemiological factors.

The common skepticism behind the health effects of artificial sweeteners lies in the long-term tests done on animals. A study conducted on an initial population of 2,500 rats administered with high doses of saccharin concluded with an increased risk of bladder cancer and neoplasias (Fukushima S, 1983). Despite this, both the FDA and SCF conclude that there is no conclusive evidence linking increased risk of death and saccharin consumption in humans. As for cyclamate, a chronic toxicity study

was conducted on a group of 80 rats (35 male and 45 female); and each rat was given either a dose of 500mg/kg, 1120mg/kg, 2500mg/kg of cyclamates. This resulted in seventy of the eighty rats developing papillary carcinomas, and also the accumulation of cyclohexylamines (CHA) (Oser BL, 1975). This strong correlation was a major breakthrough for the FDA and upon these findings, immediate action was taken; thus, cyclamate was removed from the GRAS (generally regarded as safe) status and banned within the United States in 1969. Studies for aspartame have concluded with opposite results and the FDA has deemed animal testing on aspartame irrelevant to humans conditions. Although a study linked increased development of malignant brain tumors to increased consumption of aspartame, there is no correlation seen in similar studies conducted on humans. Later generation sweeteners (saccharin, cyclamate and aspartame) have been extensively tested by the FDA and the skepticism amongst consumers today is proliferated by studies conducted on animals. Although cyclamates are now banned from consumption in the United States, it is widely used in other countries around the world. Despite this, other later generation sweeteners have maintained their GRAS status.

Studies today conclude that the effectiveness of artificial sweeteners is questionable, as evidence suggests, there may even be a risk of gaining weight. However, in terms of the health risks associated with long term artificial sweetener usage, evidence of detrimental effects associated with chronic consumption can be seen in humans (cyclamates) and animals (saccharin, cyclamates and aspartame). There is still continuing research being done on the long term consumption of new age sweeteners (stevia, sucralose, and neotame), and their safety must be determined. As of now, the FDA and SCF still conclude that a heavy dose of approved artificial sweetener (>1680 mg per day) can increase bladder cancer by 30%, and current normal consumptions are well under this amount.

Conclusion

With today's fast paced market and everyday breakthroughs in technology, artificial sweeteners have hit the market with great magnitude. How did the market for artificial sweeteners become so big? The 1950's were a time of sudden interest in dieting and vogue in women. Many consumers looked for lower calorie foods and healthier ingredient replacements. As obesity rates began skyrocketing in the 1980's, people looked for reasons why. High fructose corn syrup (HFCS) was linked and thus targeted as the reason why obesity rates were rising. Therefore, as a replacement for HFCS, artificial sweeteners began its increase in popularity. Artificial sweeteners should therefore be studied in how they relate to the food industry. Remember, the food industry revolves around inputs, processes, and outputs. In terms of inputs, agricultural commodities play an important role. Inputs of artificial sweeteners are relatively simple. Because they are chemical inputs, they will not be volatile. Crop productivity and crop safety will be safe because chemical composition will be consistent, whereas in other foods, spoiled crops may lead to bad outputs, leading to the downfall of a company. Processes of the food industry revolve around food industrial manufacturing, which is also rather reliable because sweeteners are chemically synthesized in labs, which follow very strict guidelines. However, outputs of artificial sweeteners in the food industry are where troubles may lie. As more consumers became interested in artificial sweeteners and purchased them, consumer standards increased. Therefore, food companies increased their production and allocated more money and time into the production of sweeteners. As more products emerged on the market, companies began taking different strategic marketing approaches to attract consumers to their product. Marketing gurus advertised their products in a way to mask potential uncertainty or fear in the consumer and relied a lot on words such as natural, healthy, beneficial, or advantageous. Because artificial sweeteners are still relatively brand new, a majority of the population consuming these are undereducated. Consumers must be careful with

misconceptions formed due to many various techniques that brush over the possible dangers of consuming artificial sweeteners. Once adequate education is obtained, the decision to consume artificial sweeteners lies solely in the consumer.