INTRODUCTION

The past year has seen a whirlwind of trendy diets gone mainstream. And even those of us who think that the Atkins, South Beach, or Zone have become trends of the past are still somewhat conscious of the calories we consume. Non-caloric artificial sweeteners, such as Sweet'n'Low in the pink packet and Equal in the blue packet, are being used in ever increasing quantities. They are stirred into daily lattés and found as additives in diet sodas and light yogurts. Use of artificial sweeteners dates back to the late nineteenth century, when saccharin was first synthesized as a cheaper substitute for sugar. In the 1950s cyclamate came along with an improved taste profile, and it was blended with saccharin to create Sweet'n'Low. Next came the 1981 FDA approval of aspartame, now marketed as NutraSweet and Equal, which initiated waves of new diet products (1). This concluded the era of 'first-generation' sweeteners.

Among all these old-time sweeteners, newer 'second-generation' sweeteners have been developed and are rapidly gaining popularity. In the spring of 1998, the FDA approved use of the second-generation sweetener sucralose as an additive in a variety of products (2). The following year, sucralose was approved as a general-purpose sweetener, joining the ranks of saccharin and aspartame. Key advantages of sucralose over other sweeteners include its lack of after-taste and its stability at high temperatures (3). Sucralose is now marketed under the name Splenda. Perhaps due to a clever and aggressive marketing campaign, Splenda has exploded in popularity. This newbie yellow packet has not only made its way into coffeehouses nationwide, but also the recent year-end marketing push has splashed Splenda all over television and popular magazines. In fact, Splenda's demand greatly exceeds its supply. The sole manufacturer, Tate & Lyle of London, recently announced that it could not supply Splenda to any additional companies, consequently halting new product development (4).

Despite all the excellent hype, a simple Google search for "Splenda" yields countless articles and testimonials about the dangers of its consumption. Although these reports are alarming, their claims are not supported with any rigorous scientific evidence. This report will review current literature concerning the safety of sucralose consumption.

"MADE FROM SUGAR SO IT TASTES LIKE SUGAR"

Splenda is essentially composed of the substance sucralose, which is blended with small amounts of the inert ingredients dextrose and maltodextrin, adding bulk so the product can be measured out cup-for-cup like sugar. Sucralose was developed in the 1970s by the clever Brits at Tate & Lyle and Queen Elizabeth College. Splenda is currently the only sucralose-containing sweetener. It is sold by McNeil Nutritionals, a division of Johnson & Johnson, who have a long-term contract with the product developer Tate & Lyle (4).

Sucralose is the chemical 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside. This mouthful of a molecule is synthesized from sucrose through a five-step process that substitutes three hydroxyl groups of sucrose with chlorine atoms. These selective substitutions make the new molecule extremely stable to both enzyme hydrolysis and acidic environments. In addition, sucralose is hydrophilic, with a solubility of about 25% in water (5). Another important advantage is that sucralose doesn't chemically interact with other food ingredients and is even stable in the presence of ethanol (3). Collectively, these properties make sucralose an excellent food ingredient for both industrial product developers and desperate housewives alike.

Sucralose is also very stable at room temperature, and after one year it will retain at least 99% of its original sweetness (3). This long shelf life is an additional advantage for manufacturers. Sucralose is approximately 600 times sweeter than sugar, so less volume of the molecule is necessary to achieve the same sweetness as sugar. Standardized sensory testing, conducted by trained panelists, has examined the qualities bitterness, sourness, body, residual sweet after-taste, and non-sweet aftertaste. Results showed that sucralose had a taste profile that was statistically quite similar to sugar (6).

A reasonable concern regarding chemically modified products is that they will be broken down into toxic metabolites in the body. There is concern that sucralose will dechlorinate and therefore be dangerous. In an acidic environment, sucralose will hydrolyze into two chlorinated monosccharides. The rate of hydrolysis is both temperature- and pH-dependent. A typical daily intake of sucralose is 1.1mg/kg body weight, which would yield 3.2μg/kg body weight of hydrolysis products. (3) However, there is no evidence that sucralose or any of its breakdown products dechlorinate *in vivo*, in any species (reviewed by 5). Sucralose is therefore stable in the human body and will not form toxic breakdown products.

SUCRALOSE METABOLISM

Orally ingested sucralose is minimally metabolized, and the pharmacokinetic profile of sucralose has been determined using a ^{14}C-labeled version of the compound. Eight healthy males, with a mean age of 39 years (30-48 years) and a mean weight of 79 kg (70.5-88 kg) were given sucralose at an oral dose of 1mg/kg (7). On average, humans absorb about 15% of ingested sucralose from the upper gastrointestinal tract via passive diffusion (5). Of the total radiolabeled sucralose, an average of 14.5% was excreted in the urine and an average of 78.3% was excreted in the feces. Both urinary and fecal excretion do not involve significant metabolism. More than 90% of total sucralose excreted in urine is completely unmetabolized. Two glucuronidated forms are also excreted in urine, representing 2.6% of the total oral dose (7). Distribution and elimination have only been studied in rats, using a similar radiolabeling method. Audioradiography determined that sucralose is distributed to the liver, blood, kidney, small intestine, and large intestine due to biliary excretion, and sucralose was eliminated within 6 hours. Pharmacokinetics indicate that sucralose has a human half-life of 13 hours (5). Pharmacokinetic properties of sucralose have not been studied extensively in humans, and will obviously vary greatly between individuals. Based on current literature, there is no evidence that the human body metabolizes sucralose, allowing us to add sweetness to our food without adding extra calories.

ANIMAL MODELS FOR SUCRALOSE SAFETY

Although sucralose is not significantly metabolized, we still must ask whether it's passage through the human body is a safe one. The FDA has stringent requirements for food additive approval in the United States, including assessments of the product's possible carcinogenicity, reproductive toxicology, neurotoxicity, and genetic toxicity. These studies are mostly done on animal models and it is uncommon to find extensive studies on human subjects before new products are marketed.

The dosage of sucralose given in such trials is often the maximum tolerated dose. A controlled study in rats given a mixture of sucralose and its hydrolysis products did not

find any significant difference in the occurrence of neoplasia between treatment and control groups. A similar mixture of sucralose was found neither to affect the reproductive capacity of male or female rats, nor to have teratogenic effects. Some rats were given a high-dose sucralose mixture (270 mg/kg), and evidence of maternal toxicity was documented. This dose is equivalent to 40,000 times the estimated maximum daily intake level in the United States. Sucralose metabolites were not found to have any CNS pathology in rats or marmoset monkeys (reviewed by 5).

Although animal models are unanimously accepted in the scientific community and provide evidence for product safety, clinical trials in human subjects are the only definitive method for addressing safety concerns. These trials must also be conducted using dosages that best approximate actual product consumption. Repeated administration of many completely safe and natural substances, at a dose greater than 40,000 times the average daily consumption, over a period of many days, will obviously cause metabolic disturbances and pathology.

SUCRALOSE IS SAFE FOR HUMAN CONSUMPTION

The FDA has concluded that sucralose does not pose carcinogenic, reproductive, or neurological risks to human beings (8). So, what kind of direct evidence exists regarding sucralose safety? Baird *et al.* performed a pair of sucralose tolerance studies. The first was an observational study conducted on eight subjects over a period of 17 days with an ascending dose scheme (range 1-10mg/kg body weight/day). The second was a multi-center, single-blind, randomized, controlled study on 118 subjects over 13 weeks, comparing repeated doses of sucralose (range 125-500mg/day) to fructose. Neither study resulted in any positive hematologic, serum biochemistry, urinary, cardiac, or ophthalmologic findings. Sucralose was found to be well tolerated in single doses up to 10mg/kg/day and repeated doses increasing to 5 mg/kg/day for 13 weeks (9). So, there have been no documented adverse effects due to short-term sucralose consumption.

Since diabetics are a group in need of sugar alternatives, human sucralose consumption has been studied in this population. A comparative observational study on 16 male subjects with well-controlled type 2 diabetes found that a diet incorporating fat replacers and sucralose yielded better improvements in metabolic and anthropometric variables, as compared to the currently recommended American Diabetic Association diet (10). A multi-center, double-blind, randomized, placebo-controlled study on 128 obese subjects with type 2 diabetes examined the effects of sucralose on metabolic profiles as compared to placebo. There were no significant differences between the groups in measured HbA1c, fasting plasma glucose, or fasting serum C-peptide, showing that sucralose consumption for 3 months at a dose of 7.5 mg/kg/day (estimated to be three times the average maximum intake) does not affect glucose homeostasis in type 2 diabetics (11). In summary, sucralose is well tolerated in both healthy and diabetic individuals.

RECOMMENDATIONS FOR SPLENDA CONSUMPTION

The 2004 recommendation from the American Dietetic Association states that we can safely consume nonnutritive sweeteners as part of a diet that both follows current federal nutrition recommendations, including the Dietary Guidelines for Americans and the Dietary References Intakes, and addresses individual health goals (12). To date, 172

studies have been done on sucralose. Interestingly, each study has been financed by sucralose manufacturer Tate & Lyle, distributor McNeil, or their representative organizations (4). Currently, there is no direct clinical evidence that sucralose has harmful effects in humans. However, the product has not existed long enough to assess its long-term effects. Consequently, no long-term safety studies have been performed. New sucralose-containing products will be put out as fast as Tate & Lyle can supply the sweetener. Everything from children's cereals to energy drinks now contains Splenda.

With Splenda's ever-increasing presence in the American diet, it is imperative that an independent, unbiased research group conduct a large-scale, randomized, placebo-controlled trial to assess the long-term safety profile of Splenda in both children and adults. This is the clinical gold standard and the only way to truly assess the product's safety. A relevant historical example is the story of the original Sweet'n'Low duo saccharin and cyclamate, which were each found to be carcinogenic in animals. Cyclamate was banned by the FDA in 1970 but has been widely used in other countries since its invention over 50 years ago. And for many years, based on one of 20 indirect studies performed, saccharin-containing products carried a carcinogenic warning on their labels. Long-term, controlled trials eventually determined that these sweeteners are not carcinogenic (reviewed by 1). So we cannot know the truth about Splenda until it's old enough to be studied in a long-term context.

Various case reports have surfaced regarding adverse reactions to Splenda consumption. While such reports can be informative, they cannot accurately represent the product's safety in the way a rigorous scientific assessment can. Moreover, some individuals may be expected to have adverse reactions to Splenda – just as some individuals have allergic reactions to natural foods including dairy products, shellfish, and peanuts. Case reports do not define product safety, and such individual reactions must be distinguished from toxic characteristics of the product itself.

Splenda should be used in moderation, like any other dietary additive or supplement. As with any new product, people should use Splenda cautiously at first, and seek medical attention if they experience any unpleasant symptoms. Thus far, Splenda has proven to be a safe and sweet alternative to sugar.

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