




## *Sucralose: A Scientific and Safety Review*

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PROFESSIONAL PRODUCT INFORMATION



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This paper provides a scientific and safety review of sucralose, one of the more recent additions to the category of no-calorie sweeteners. It is commercially available as SPLENDA® Brand Sweetener and is the no-calorie sweetening ingredient in all SPLENDA® Sweetener Products. McNeil Nutritionals LLC, a Johnson & Johnson company, markets nutrition and health related products including SPLENDA® Sweetener Products. Tate & Lyle PLC sells sucralose as an ingredient to food and beverage manufacturers.

The obesity epidemic, as well as the related rise in type 2 diabetes among adults and children, makes it important to identify, assess and use a variety of weight management approaches. The use of sucralose (SPLENDA® Brand Sweetener) may help patients control caloric intake. Sucralose may also be a useful tool in the management of sugar intake for other health purposes, such as not promoting tooth decay.

## KEY POINTS

- Sucralose was the subject of extensive safety testing, representing over 20 years of research and including more than 100 studies. Regulatory, health and food safety authorities from around the world have concluded that sucralose is safe. Sucralose is approved for use in over 80 countries, and is used in more than 4000 products worldwide.
- The chemical structure of sucralose, a substituted (chlorinated) disaccharide, has features key to its safety:
  - Sucralose is a small, relatively inert molecule:  
*Stable in vivo:*
    - Is largely unabsorbed
    - Is not broken down for energy or to smaller chlorinated compounds
    - Does not dechlorinate
  - Sucralose is highly water soluble and poorly soluble in fat:
    - Does not bioaccumulate
    - Is eliminated quickly
- Pre-approval and post-marketing intake assessments indicate that consumption levels are well below long-term intake averages denoted as safe by regulators.
- Sucralose safety studies include multi-species, multi-generational, and environmental research. Safety outcomes reflect the stability and poor lipophilic nature of sucralose. Pharmacokinetics and safety research show the following:
  - The vast majority (85%) of consumed sucralose is not absorbed and is excreted in the feces unchanged. Limited absorption (approximately 15% of a consumed dose) is by passive diffusion and not by active or facilitated uptake, as with digested disaccharides.
  - Sucralose is not a substrate for either oral bacteria or gut flora; thus, there are neither dental consequences nor GI side effects like those sometimes found with some unabsorbed, but fermentable, substances (e.g., sugar alcohols).
  - A small portion (2%) of consumed sucralose, which passively crosses to the blood stream, is converted to two glucuronide conjugates. Those conjugates are readily excreted in human urine and pose no safety concern.

- Radiolabel studies show that sucralose is also not actively transported from the bloodstream across other membranes. Studies indicate that sucralose is not actively transported into breast milk, across the placenta into the fetus or across the blood-brain barrier into the nervous system.
- Additional studies have shown that the molecule does not bind to proteins, strictly limiting potential for longer elimination times and/or reactivity. Sucralose is not a protein and studies show no allergic potential.
- The chemical structure of sucralose dictates its distribution characteristics. Being a rather small (MW 400) water-soluble molecule that is not lipophilic, the sweetener follows body water and is quickly eliminated.
- Safe use is expected in all segments of the population, based on both acute and long-term studies.
  - No acute toxicity was found at doses up to 10 to 16 g/kg in rodents (equivalent to the sweetness of 1000 pounds of sugar for a 175 pound adult).
  - No chronic toxicity was found in repeated administration studies in which high doses of sucralose (doses hundreds of times greater than maximum estimated daily intakes and 800-1300 times greater than the Estimated Daily Intake [EDI]) were given daily for up to a lifetime. Repeated administration studies cover all phases of life, from pre-conception through aging adulthood, and include multi-generational research.
    - No toxicity was observed relative to growth and development, hematology, clinical chemistry, urinalysis, ophthalmologic evaluations, neurological health, immunologic assessments, reproductive indices, gross evaluations or microscopic evaluations, including full histopathology.
  - Sucralose has been found to be non-carcinogenic. Lifetime studies were conducted in two different species, mice and rats, both shown to be good models for humans in terms of how the body handles sucralose. Both studies utilized doses more than a thousand times the level that people would consume on a daily basis and showed that sucralose is non-carcinogenic.
  - Sucralose is safe for the environment, as demonstrated in studies in invertebrate and vertebrate aquatic species and algae and microorganisms.

Some web misinformation exists regarding the effects of sucralose on certain tissues. This, however, appears to be related to incomplete and/or erroneous characterization of safety studies conducted. Trusted sources can be accessed to provide reliable information, such as [www.SPLENDATruth.com](http://www.SPLENDATruth.com) , [www.SPLENDA.com](http://www.SPLENDA.com) and the detailed FDA preamble discussion (<http://www.cfsan.fda.gov/~lrd/fr980403.html>) that accompanies publication of the regulations\* for sucralose.

Conclusion: SPLENDA® Brand Sweetener (sucralose) can be used safely by all segments of the population, including, but not limited to, women who are pregnant or nursing, children and people with diabetes.

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\*<http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=d9c370a3a322d9e2df34d4f52fdc608a&rgn=div8&view=txt&node=21:3.0.1.1.3.9.1.20&idno=21> and <http://www.fda.gov/OHRMS/DOCKETS/98fr/081299b.pdf>

## INTRODUCTION

No-calorie sweeteners have been available in the U.S. since 1903 with the introduction of saccharin, and there are currently five no-calorie sweeteners permitted for use by FDA, including acesulfame potassium, aspartame, neotame, saccharin and sucralose.<sup>1,2</sup> No-calorie sweeteners have long been a means of helping people reduce sugar intake and the calories from sugar. However, recent trends reflecting increased sugar intake may make it important for both consumers and healthcare providers to consider additional strategies to reduce intake of added sugars in the diet.

The average added sugar intake in the U.S. is currently estimated to be approximately 300 calories per day,<sup>3,4</sup> a significant portion of the average daily diet. Excessive caloric intake along with insufficient caloric expenditure are key factors in the development of overweight. The USDA guidelines state: “Beverages with caloric sweeteners, sugar and sweets, and other sweetened foods that provide little or no nutrients are negatively associated with diet quality and can contribute to excessive energy intakes, affirming the importance of reducing added sugar intake substantially from current levels.”<sup>5</sup>

Overweight and obesity are currently major public health concerns in the U.S. and throughout the world. In the U.S., over 60% of adults are overweight,<sup>6</sup> and worldwide, over 300 million people are obese (BMI > 30).<sup>7</sup> Increased risks of developing diabetes, heart disease, certain types of cancer, and several other serious chronic health conditions are well documented.<sup>8</sup> In the U.S., related healthcare costs have also become a significant economic burden.<sup>9-11</sup>

Pediatric obesity is now recognized as a major medical and public health problem throughout the world.<sup>12,13</sup> Children who are overweight are also at increased risk of being overweight as adults,<sup>12</sup> and are at increased risk of certain health complications even while still in childhood.<sup>12,14,15</sup> Notably, the current dramatic increase in type 2 diabetes among children is related to the increase in childhood overweight.<sup>16</sup> Recent research also indicates that 20-25% of non-diabetic, very obese children have pre-diabetes.<sup>17</sup> Children who are overweight are also at significant risk of suffering from lower self esteem.<sup>18,19</sup>

The seriousness of the risks of overweight and its current prevalence demand close attention to all possible strategies for both excess weight prevention and weight reduction. Children may be a critical audience to address to help prevent overweight in adulthood.

In addition to potential assistance in calorie management, management of sugar intake through no-calorie sweeteners may be helpful in dental health and in carbohydrate management for people with diabetes.

People are increasingly turning to healthcare providers for answers to issues regarding weight management and diabetes, and have questions regarding the use and safety of no-calorie sweeteners. More and more people rely on sources of information that are not always credible, such as the Internet, including websites and chat rooms. These sources may have misleading and erroneous information, resulting in unnecessary patient concerns.

This paper provides a detailed scientific and safety review of the no-calorie sweetener, sucralose.

## BACKGROUND

SPLENDA® Brand Sweetener (sucralose) was the subject of extensive safety testing, representing more than 20 years of research and including more than 100 studies. Regulatory, health and food safety authorities from around the world have concluded that sucralose is safe.

In 1991, the Health Protection Branch of Health and Welfare, Canada was the first national regulatory body to permit sucralose for use. Similarly, every other reviewing agency has similarly concluded that sucralose is safe for use as a sweetener, including authorities such as the United Nations' Joint (Food and Agricultural Organization/World Health Organization) Expert Committee on Food Additives (JECFA), the U.S. Food and Drug Administration (FDA), the Scientific Committee on Food of the European Union (SCF), and Food Standards Australia-New Zealand (FSANZ).

In discussing its sucralose regulation (FDA Talk Paper T98-16, 1998), the FDA states: “In determining the safety of sucralose, FDA reviewed data from more than 110 studies in humans and animals. Many of the studies were designed to identify possible toxic effects including carcinogenic, reproductive and neurological effects. No such effects were found, and FDA’s approval is based on the finding that sucralose is safe for human consumption.”<sup>20</sup>

Similarly, from the Opinion of the Scientific Committee on Food of the European Commission on Sucralose: “There is adequate evidence, [for sucralose], that there are no concerns about mutagenicity, carcinogenicity, development or reproductive toxicity.”<sup>21</sup>

More than 80 countries now permit the use of sucralose, all without any requirement for any type of warning label. Sucralose has been in use since 1991 and, internationally, no regulatory concerns have developed.

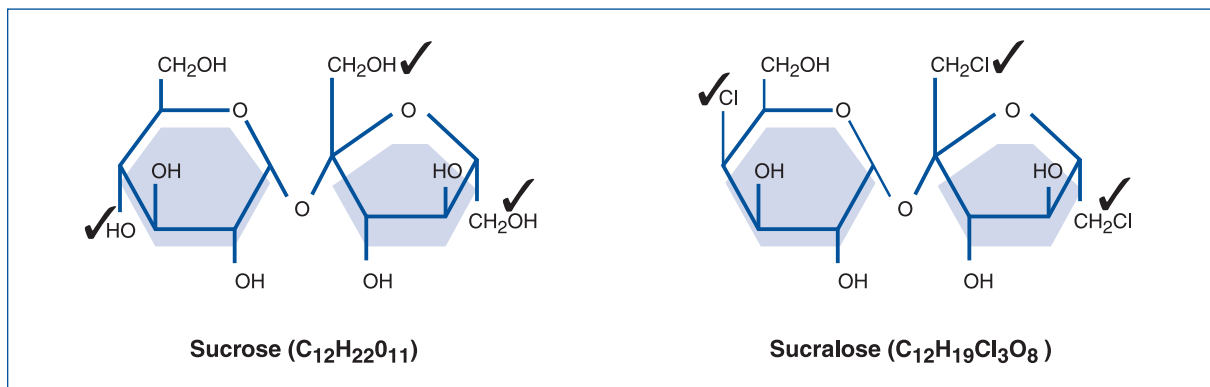
A panel of 16 independent, well recognized, non-governmental scientific experts also reviewed the sucralose safety database and concluded it to be safe for its intended use.<sup>22</sup> This panel represented significant expertise across a wide range of health and safety disciplines, including areas such as general toxicity, reproductive toxicity, mutagenicity, carcinogenicity, pharmacokinetics, immunotoxicity and neurotoxicity.

Much of the sucralose safety data is the subject of peer-reviewed publications discussed herein, and all of the data, including the independent panel assessment, is available through the sucralose food additive petition filed with FDA and other regulatory agencies.

## DESCRIPTION

### Chemical structure

Sucralose is a white crystalline solid, made from a process that starts with sugar (sucrose) and selectively substitutes three atoms of chlorine for three hydroxyl groups on the sugar molecule, which involves inversion of the configuration at carbon-4 from the gluco- to the galacto-analogue.<sup>23</sup> (Figure 1) The resulting molecule, 1,6-dichloro-1,6-dideoxy- $\beta$ -D-fructofuranosyl-4-chloro-4-deoxy- $\alpha$ -D-galactopyranoside, like sucrose and other disaccharides, is small (MW ~400) and highly water-soluble. It is not lipophilic.



(Figure 1)

### Taste

Sucralose has been shown to have a taste similar to sugar<sup>24</sup> without the bitter aftertaste that has been associated with some other no-calorie sweeteners, such as saccharin and acesulfame K.<sup>24-26</sup>

A recent study also suggests that sucralose interacts with sweet taste receptors similarly to natural sugars by interaction with the same two sweet taste receptors with which sugar interacts.<sup>27</sup>

Although recognized by the same sweet taste receptors, sucralose, like other popular no-calorie sweeteners, is intensely sweet, about 600 times sweeter than sugar. In comparison, aspartame, saccharin and acesulfame K are about 200 times sweeter than sugar, while neotame, an aspartame-derivative, is about 8,000 to 12,000 times sweeter than sugar.<sup>28</sup> *Intense sweetness means that intake will be substantially less on a weight-for-weight basis compared to sugar.*

### Stability

To derive energy from sucrose and other disaccharides, all mammals begin digestion in the gastrointestinal tract. Disaccharidases hydrolyze the central oxygen bond that links the two component monosaccharides. This bond is called the glycosidic linkage (see Figure 1). Upon hydrolysis, the resultant monosaccharides are quickly taken up into the bloodstream, typically by facilitated or active transport.<sup>29</sup>

The presence of the chlorine at the specific sites on the sucralose molecule stabilizes the glycosidic linkage to such enzymatic hydrolysis. This is demonstrated in *in vitro* studies of a wide range of disaccharidases. *In vivo* radiolabel studies also show that no monosaccharide derivatives are formed; that any sucralose absorbed is absorbed only by passive diffusion; and that sucralose is not otherwise broken down for energy and is, therefore, non-caloric. Radiolabel studies also show that sucralose is not dechlorinated.

While some no-calorie sweeteners can quickly lose sweetness with heat, sucralose has excellent stability to the high heat of cooking and baking, and even to ultra-high temperature (UHT) pasteurization.<sup>30</sup> Thus, foods and beverages made with sucralose do not lose their sweetness over time or with cooking and baking. SPLENDA® No Calorie Sweetener products, however, do not possess all the characteristics of sugar in cooking and baking. For example, sucralose does not caramelize like sugar, so it will not produce the browning characteristic of some baked goods. Patients can be referred to the manufacturer's website for information on cooking and baking, for optimal product satisfaction.

## CLINICAL AND PRE-CLINICAL SAFETY EVALUATIONS

A large number of standard and unique safety studies were conducted to evaluate the safety of sucralose. These studies provide a picture of the safety of sucralose at doses hundreds, if not thousands of times, the level of projected human consumption.

**ADME** - A series of studies evaluating the Absorption, Distribution, Metabolism, and Elimination (ADME) of sucralose was assessed in both human and animal studies. The data from these studies clearly reflect the stability and poor lipophilic nature of sucralose -- key attributes to sucralose's safety.

- The **absorption** of sucralose in humans is limited, with approximately 15% of the consumed dose passively absorbed from the GI tract.<sup>31</sup> There is no active transport across the brush border. Although absorption levels can vary considerably between individuals, observed absorption levels for humans are bracketed by the range of absorption levels seen in animal model studies, with rats, mice and dogs absorbing, on average, 10%, 30%, and 35%, respectively.<sup>32</sup> Pharmacokinetic evaluations across all species tested, including rats, dogs and humans, showed that the rapid, albeit small, elevations in blood level following consumption are consistent with upper GI absorption,<sup>33</sup> although diffusion across large intestinal membranes has also been observed.<sup>34</sup> The absorption characteristics of sucralose are consistent with a small molecular weight, non-reactive and hydrophilic molecule.
- The chemical structure of sucralose also dictates its **distribution** characteristics, it being a rather small (MW 400), water-soluble molecule that is not lipophilic.<sup>33</sup> Radiolabel studies show that sucralose passively follows body water and is distributed to essentially all tissues. There is, however, no evidence of active transport. Radiolabel studies also specifically indicate that the small amount of sucralose that enters the circulation is not selectively or actively transported into milk or across the placenta into the fetus or across the blood-brain barrier into the nervous system.<sup>32,33</sup>
- Sucralose is not **metabolized** for energy in any tested mammalian species<sup>34,33,35-37</sup> and is, therefore, non-caloric. Further, studies show that sucralose is not perceived by the body as a carbohydrate:
  - Sucralose is not a substrate for, nor does it interfere with the activity of, numerous types of disaccharidases.<sup>38</sup>
  - Specialized carbohydrate metabolism studies in rats with varying routes of administration and doses, including intravenous doses up to 500 mg/kg, showed no effect on insulin levels, utilization and steady state levels of glucose and/or fructose, lactate synthesis and use, and other measures.<sup>39</sup>

- High-dose, repeated administration studies in both normoglycemic individuals and people with diabetes demonstrate no effect of sucralose on glycemic status or control, as measured by insulin or c-peptide (validated *in vivo* marker for insulin secretion) levels, post-prandial or fasting blood glucose levels, or percent glycosylated hemoglobin (HbA1c).<sup>40-42</sup>
- Sucralose is a substrate for neither oral bacteria<sup>43</sup> nor gut flora.<sup>38,44</sup> Radiolabel studies also show no adaptation of gut flora over time.<sup>33</sup>

A small portion (approximately 2%) of consumed sucralose is converted to two glucuronide (sugar-acid) conjugates.<sup>31,33,35,36</sup> Like unchanged sucralose in the bloodstream, these conjugates are readily excreted in human urine (see **Elimination** below), and studies show that they pose no safety concern.<sup>32</sup>

- **Elimination** of sucralose is similar for humans and the relevant animal models.<sup>31,33,35,36,45</sup> In humans, the vast majority (85%) of consumed sucralose is excreted in the feces unchanged, without any GI effects.
  - The absence of GI effects could be anticipated because: 1) unabsorbed sucralose is not metabolized by gut flora to yield gaseous by-products, and 2) because of its highly intense sweetness, overall sucralose intake is so low that the potential for any adverse osmotic effect in the gut is self-limiting. (Sucralose is approximately 600 times sweeter than sugar, so that average excessive intakes are in the range of about -1.5 to 2.4 mg/kg. This means that for a 175-pound adult, unabsorbed sucralose would only be about 80-200 mg.)

Of the small amount of sucralose that crosses into the bloodstream, which is excreted largely as unchanged sucralose (see **Metabolized**, page 7), all is eliminated via the urine, consistent with sucralose's hydrophilicity. In all species tested, including humans, over 95% of the consumed dose is excreted either in the feces (unabsorbed fraction) or urine (absorbed fraction) as unchanged sucralose. The experimental findings also indicate that sucralose has a relatively rapid elimination, reaching peak plasma level in 1.5 to 3 hours with an effective half-life of approximately 13 hours, precluding accumulation. In a 13-week study in humans, with ascending doses of 1, 3, and 7 mg/kg/day for 3, 4, and 6 weeks, respectively, there was no trend towards increasing plasma concentration.

**Acute Toxicity** – Acute toxicity was assessed in gavage studies, which allowed for extremely high doses of sucralose at a single intake. These studies showed no adverse effect of sucralose in rats or mice at the highest doses tested, or approximately 10-16 g/kg.<sup>46</sup> This amount of sucralose is equivalent in sweetness to about 13 lbs of sugar/kg, or 1000 pounds of sugar-sweetness, for a 175-pound adult. For a child of 40 pounds, this amount is equivalent in sweetness to about 240 pounds of sugar at a single intake. These data are useful in providing confidence that no toxicity would likely occur due to an accidental consumption of a large amount of sucralose.

**Subchronic and Chronic Toxicity** – As described above, numerous subchronic and chronic toxicity studies in relevant animal models were conducted, covering all phases of life and at doses hundreds to thousands of times greater than both average and maximum estimated daily intakes in humans. Additional animal studies supported these general toxicity

assessments and include specific studies in such areas as diet palatability, immune function, allergenic potential, and neurological health. As discussed below, safety is supported by these assessments and also by all levels of clinical studies conducted (see **Clinical Studies**, page 11).

**Subchronic toxicity** was generally assessed in two relevant species: rats and dogs.<sup>46</sup> These studies showed no direct adverse effects of sucralose. There were some indirect effects observed in extremely high-dose dietary studies conducted in rats, which were considered related to effects on diet palatability.<sup>32,47</sup> Studies showed that rats would find such extremely sweet diets less palatable than the control diet.<sup>32,47-50</sup> Poor diet palatability was found to result in lower food intake and body weights compared to control animals and, in turn, some effects on organ weight, function and histopathologic appearance were observed. Gavage studies in which sucralose was administered by stomach tube, and isocaloric pair-feeding studies, however, confirmed that these were not toxic effects of sucralose, but the consequences of poorer diet palatability and lower food consumption.<sup>32,46,51-54</sup> When sucralose was given by gavage, thus bypassing the taste receptors, at the same doses (over a thousand times the estimated daily intake) and for the same comparable durations, rats ate as much food, gained as much weight and had none of the anticipated palatability-related effects on food consumption or body or organ weight seen in the dietary studies, and there was no evidence of toxicity. Similarly, when control rats were pair-fed to sucralose-treated rats, i.e., with the same reduced caloric intake, there were no meaningful differences between groups in food consumption, body or organ-weights or any other relevant measures of safety at these same high dose levels.

Other subchronic investigations included a study in primates to evaluate potential neurologic toxicity, including electron micrograph evaluations,<sup>55</sup> and studies in rats to assess such things as allergenicity potential and potential for effects on immune function and/or response to stress.<sup>56-58</sup> In all these studies, conducted at doses hundreds of times greater than the estimated daily intake, sucralose had no adverse effects. In particular, allergenicity was not predicted based on the nature of sucralose: sucralose is neither a protein nor a large or otherwise reactive molecule and does not bind to proteins. Immune function tests also showed that sucralose evokes no increases in immunoglobulin concentrations, including IGE.<sup>58</sup>

**Chronic toxicity** was assessed in two relevant species, rats and mice, at doses more than a thousand times the EDI.<sup>51,59</sup> Blood and urine sampling and ophthalmologic examinations were made at regular in-life intervals, and terminal assessments were made on all animals. These included both gross and microscopic evaluations of over 40 tissue types, as well as any tissue with an observed abnormality, including full histopathology. Chronic toxicity assessments show that sucralose has no adverse effects on:

- general health,
- growth and development,
- hematology and blood chemistry,
- urinalysis,
- ophthalmologic evaluations,
- neurologic health,
- immune function,
- organ and tissue appearance, or
- survival.

**Reproduction, Growth and Development** – Numerous studies were conducted to evaluate the potential for effects on fertility or reproduction, sperm glycolysis, teratogenic potential, and growth and development.<sup>46,51,59-61</sup> One of the most important of these studies was a multi-generational reproduction and fertility study conducted in rats. In this study, adult male and female rats were fed a diet containing high levels of sucralose (equivalent to 1,500 mg/kg/day) for ten weeks (males) or two weeks (females) prior to mating to provide exposure during gamete maturation. They were then mated and remained on a sucralose diet throughout gestation, parturition and lactation in order to evaluate all levels of reproductive health and performance. Pregnancies were carefully followed and full assessments made on gestational health, duration of gestation, and pup health and development. The 1st generation (F1) pups were raised by their mothers and then weaned to the same diets that their mothers consumed. As with the parental generation, randomly selected male and female F1 pups were raised to adulthood while still consuming a sucralose diet, and mated to produce a subsequent generation of offspring (F2). Once again, all evaluations of mating, fertility, reproductive health and pup health were assessed. The two generations produced showed no adverse effect of sucralose on any of these parameters.

Separate studies specifically examined the potential effect of sucralose on embryo-fetal development by feeding high sucralose diets to pregnant rats and rabbits during the period of embryogenesis (from implantation through closure of the palate). Fetuses removed by C-section were extensively evaluated for normal development, not only by external observation, but also by examining all internal soft tissues and skeletal development for each and every fetus. These studies on hundreds of fetuses revealed no birth defects or any other effect that would compromise normal embryo-fetal development, and confirmed that sucralose has no teratogenic potential. The combination of these fertility and teratogenicity studies demonstrate that consumption of sucralose has no effect on normal reproductive, fetal or neonatal health.

These results are also supplemented by the carcinogenicity studies in which rats were exposed to sucralose from conception (via exposed mothers) through to aging adulthood for their entire lifespan with no adverse effect. These combined studies show that sucralose poses no risk to general health, growth and development.

**Carcinogenicity** – The potential for new products to induce or promote neoplasia is a serious concern, and numerous approaches are taken to evaluate that potential. Short-term tests for carcinogenic potential (genetic toxicity) were conducted early in the sucralose safety assessment program.<sup>46,47</sup> These results indicated that the product was not genotoxic, i.e., that sucralose did not cause mutations or chromosome damage. Carcinogenic potential was subsequently assessed in more definitive *in vivo* studies.

Two lifetime carcinogenicity studies were conducted on sucralose, one in the mouse<sup>59</sup> and one in the rat.<sup>51</sup> Both species are generally good physiologic models for humans, and are good models in terms of how the body handles sucralose (see **ADME**, page 7). Together, they are good predictors of human carcinogenesis. In addition, proper conduct of carcinogenicity studies requires that they be performed at the maximum tolerated dose, or at doses at least 1000 times the estimated human consumption level, to maximize the potential of the agent to cause cancer or other lesions. Both sucralose carcinogenicity studies utilized sufficiently high dose levels with average lifetime daily intakes of 1,500 mg/kg/day in the rat and 3,000 mg/kg/day in the mouse. They also included detailed histopathologic analysis of all abnormalities.

Both of these rigorous lifetime studies showed that sucralose is non-carcinogenic. At doses more than a thousand times the EDI, sucralose did not promote tumor formation, affect the time to natural tumor onset, or adversely affect survival rates and/or lifespan.

### Clinical Studies in Adults, Adults with Diabetes, and Children

**Tolerance** – Clinical studies were done to supplement the standard safety assessments conducted in appropriate animal models that are required by regulators. The pharmacokinetics of sucralose in humans was also assessed to validate the utility and appropriateness of the animal models used. In humans as in animals, sucralose is largely unabsorbed and relatively rapidly excreted. There is no bioaccumulation or trend for increasing plasma levels over time with repeated use (See **ADME**, page 7). The fate of sucralose in humans is consistent with its high water solubility, poor solubility in fat, stability to enzymatic hydrolysis and dechlorination and general non-reactivity.

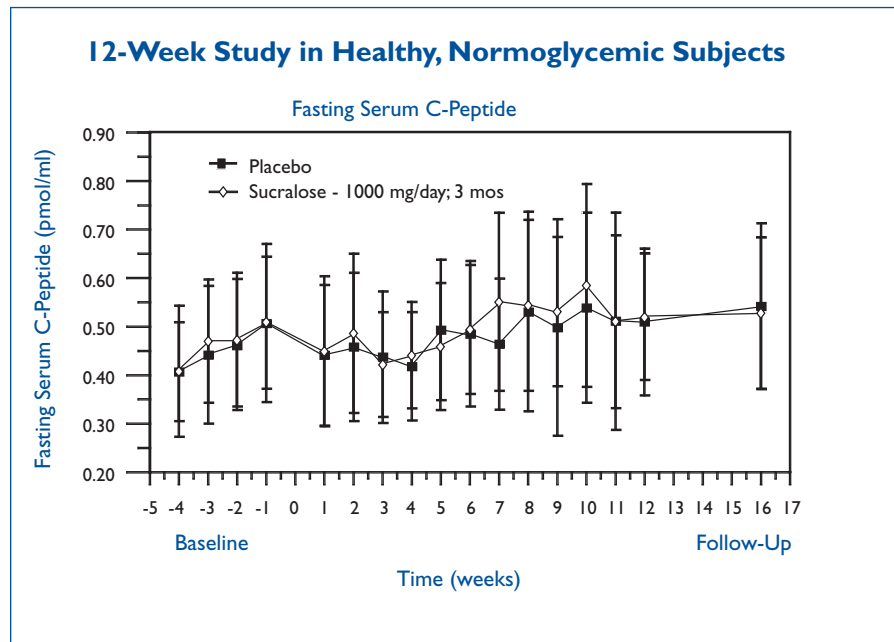
Tolerance was specifically assessed in a 13-week ascending dose study in both males and females<sup>45</sup> and in a 12-week study conducted in normoglycemic men.<sup>42</sup> Safety was also assessed in a three-month, follow-up multi-center study in people with type 2 diabetes.<sup>41</sup> These studies showed that sucralose was well tolerated at the doses given (2-4 times the maximum EDI) and not meaningfully or significantly different from controls in reported adverse health events, concomitant medications, including diabetes therapy, hematology, blood chemistry and urinalysis. Additionally, these studies did not indicate any overall health concerns from any other measures taken.

A study in overweight children looking at the potential utility of sucralose in a ‘small-steps’ diet and exercise program showed at 6 months that significantly more children maintained or lowered their BMI-percentile-for-age when engaged in this program. Although vigorous safety assessments were not included as a part of the study, there were no obvious indications of safety concerns based on compliance or known adverse events.<sup>62</sup>

Sucralose has also been used as a potential clinical diagnostic tool in patients with impaired gastrointestinal permeability.<sup>34, 63-66</sup> In these studies, sucralose was reported to be given at bolus doses in amounts far above amounts ever anticipated with food intake (up to 5 g/dose reported). Urinary or blood sucralose levels were evaluated compared to control as a marker of impaired permeability. With impaired permeability, there is the potential for increased, dysregulated solute crossing from the GI lumen to the bloodstream, resulting in increased exposure to many different solutes. Studies in the published literature indicate no overt safety concerns with the potential diagnostic tool, although safety of the diagnostic tool does not appear to be a measured endpoint.

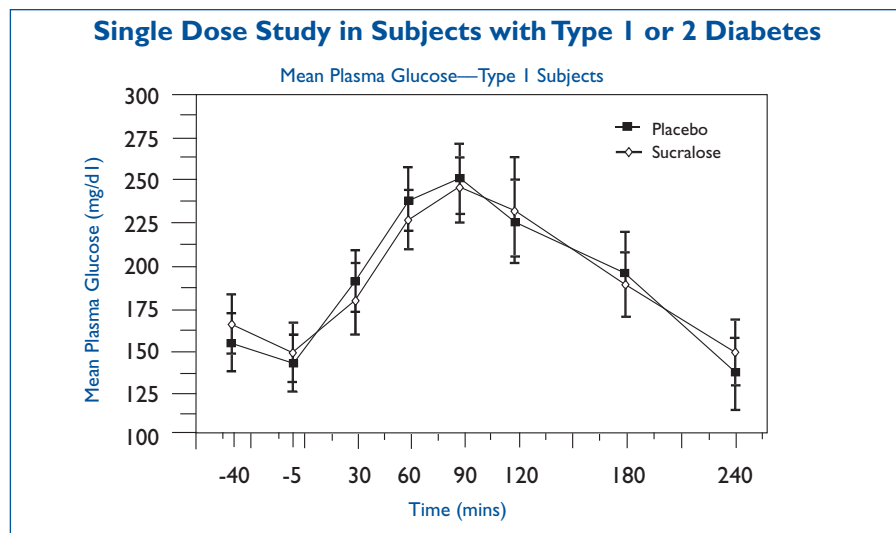
**Glycemic Control** – Potential effects of sucralose on glucose control were evaluated in both normoglycemic individuals and in people with diabetes.

A 12-week study in normal males was conducted as this population was considered to be the optimal model for detection of possible effects on perturbations in glucose control.<sup>42</sup> (Figure 2) Healthy, normal weight males, without history of diabetes, were selected to eliminate the complications of normal estrus-related hormonal variation in females, and diminish the potential effects of inherent metabolic aberrances with overweight or diabetes family predisposition, that could potentially make small changes in insulinemic response more difficult to detect. The study assessed both fasting status after daily repeated exposure to sucralose (1000 mg/day) and the metabolic response to oral glucose tolerance tests. The primary endpoint was c-peptide, the optimum measurement of insulin response, while glucose, HbA1c and direct insulin measures were also taken. At doses four times the maximum EDI, no perturbations in insulin sensitivity were shown and there was no impact on glucose control.



(Figure 2)

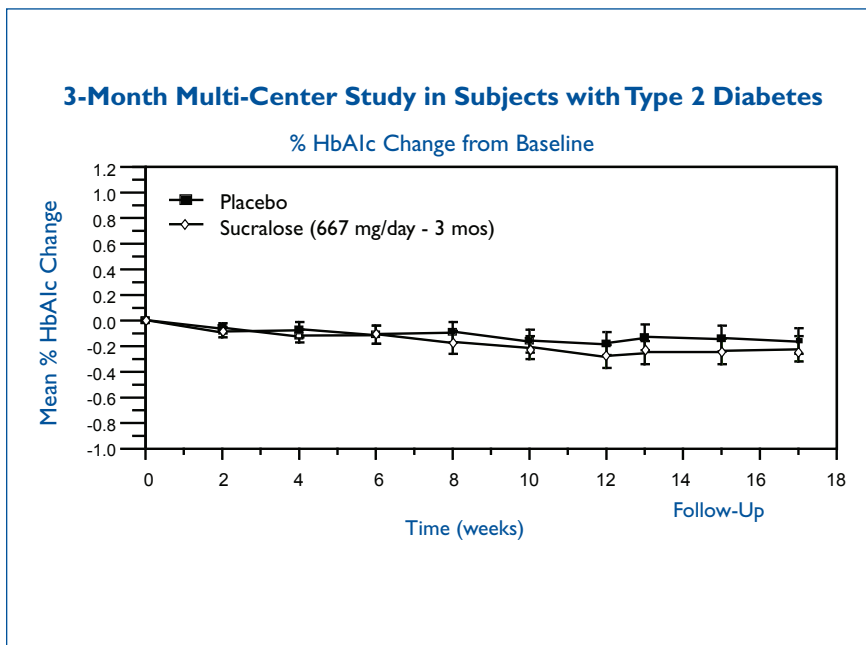
The effect of sucralose in people with diabetes was initially assessed in a single exposure, high-dose study in males and females with either type 1 or type 2 diabetes.<sup>40</sup> (Figure 3) In either population type (type 1 or 2 diabetes), there was no significant difference between sucralose and placebo subjects in the metabolic response to a standardized meal.



(Figure 3)

A 3-month, multi-center study was later conducted in individuals with type 2 diabetes.<sup>41</sup> (Figure 4) Doses were approximately 7.5 mg/kg/day of sucralose, or about three times the maximum EDI. This study demonstrated no effect of sucralose on glycemic control, fasting blood glucose, HbA1c or c-peptide. The power to detect a clinically meaningful change in the primary endpoint, % HbA1c change from baseline (0.6 between-group difference), was >99%. Additionally, the study showed that the consumption of sucralose would not interfere with patients' usual diabetes therapy.

The studies designed to detect the potential for effects on glucose control and other research have also shown that sucralose has no effect on the monitoring of either glucose (in blood or urine) or HbA1c. Like disaccharidases (see **Stability**, page 6), the enzymes involved in glucose and HbA1c assay methodologies do not recognize sucralose as a substrate, so there is no effect on monitoring.<sup>67-68</sup>

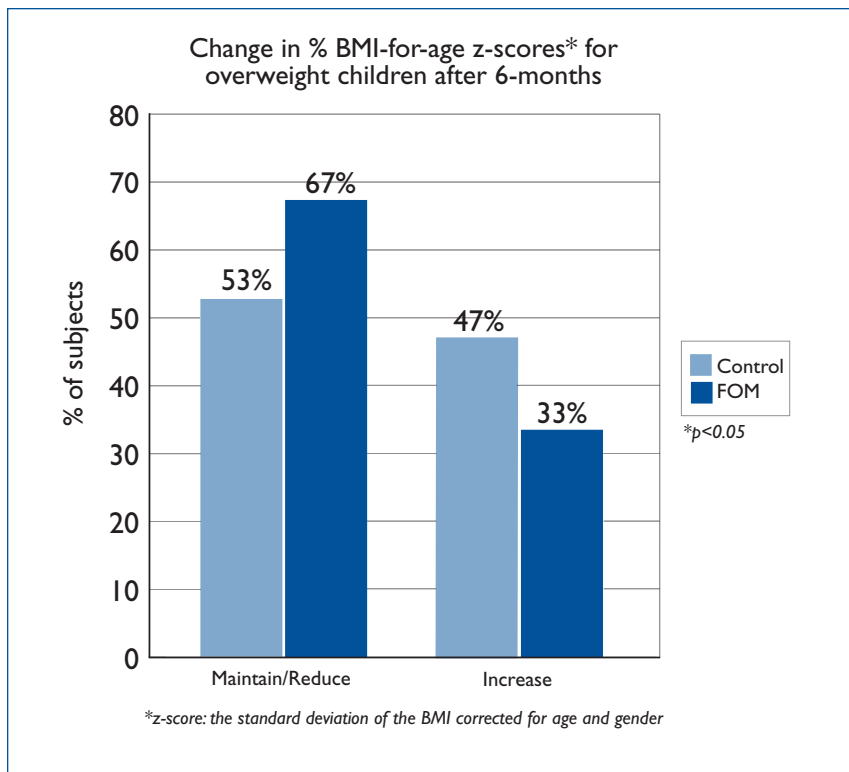


(Figure 4)

**Use in Caloric Control** – Other research has shown that no-calorie sweeteners can be used to achieve caloric reduction and, within a healthy diet and exercise program, help to achieve lower body weights.<sup>69-77</sup> People using no-calorie sweeteners may also have improved micronutrient intake vs. those who do not.<sup>78</sup> A ten-week study in overweight adult subjects also showed that those using diets containing no-calorie sweeteners vs. those who did not had improved body weight, fat mass, and systolic and diastolic blood pressure.<sup>79</sup>

These studies did not include use of products containing sucralose, but are supportive and logically related to use of sucralose.

A study in overweight children was conducted assessing the utility of a lifestyle modification program, including small changes in both physical activity (increase of 2,000 steps/day) and diet (target caloric decrease of 100 kcal/day). Subjects were given direction to achieve calorie decreases primarily by decreasing sugar intake through the use of SPLENDA® No Calorie Sweetener retail products and/or reduced calorie beverages sweetened with SPLENDA® Brand Sweetener.<sup>80</sup> Initial (six-month) data indicate that the program may be used successfully in some children to help maintain or lower BMI-percentile-for-age. (Figure 5) The significance of these results is enhanced by the known risks of overweight and the benefits of decreasing risk by preventing and/or decreasing excess body weight.



(Figure 5)

## SPECIAL TOPICS

**Dental Caries** – Because of its close chemical relationship to sugar, clinical studies were conducted on sucralose to determine if sucralose could have an impact on dental caries. *In vitro* and caries animal model studies preceded clinical studies, demonstrating no effect on bacterial metabolism and no ability to induce or promote dental caries. Subsequently, three clinical studies on the pH of human plaque *in vivo* were performed, concluding that sucralose is not acidogenic, and is therefore non-cariogenic.<sup>43</sup> Sucralose was approved by FDA for a non-cariogenic dental health claim on March 29, 2006.<sup>81</sup>

**Chlorine** – As discussed earlier (see **Description, Stability** and **ADME**, pages 6-7), sucralose is made from sugar by the substitution of chlorine atoms for hydroxyl groups on the sugar molecule. Chemically, then, sucralose is a substituted (chlorinated) disaccharide and it is sometimes referred to as a chlorinated carbohydrate. A very different class of compounds, called chlorinated hydrocarbons, such as PCB, is known to exert toxic effects. Because of the similarity in names, sucralose is sometimes confused as one of these types of compounds. However, sucralose is not at all like these substances, which are highly fat soluble, accumulate in body fat stores, and build up in the food chain leading to their toxic effects. Sucralose, in contrast, is extremely poorly soluble in fats, does not bioaccumulate either in fat stores or in the food chain, is environmentally safe, and has been shown to be safe for use in people at extremely high doses. As previously discussed (see **ADME**, page 7), sucralose also does not undergo dechlorination and is not broken down to smaller chlorinated compounds *in vivo*.

**Acceptable Daily Intake (ADI)** – Although regulators in different jurisdictions may use slightly different strategies in how they calculate ADI, they always set it significantly below levels found to be safe in the relevant animal models.<sup>77,82</sup> Thus, ADI is not a toxicity threshold. Rather, it is a level shown to be safe by a wide margin, and, in all cases, represents a 100-fold safety factor for sucralose. This safety factor is employed to account for possible differences between species and between individuals. For sucralose, regulatory officials around the world have set the ADI from 5 (U.S.) to 15 (EU, Australia) mg/kg bodyweight per day. Importantly, ADIs are also based on chronic consumption. For example, a child progressing from 50 pounds to 100 pounds would need to consume about 3 to 8, eight-ounce glasses of diet drink daily and up to 6 to 16, eight-ounce glasses of diet drink daily to reach the 5 to 15 mg/kg/day ADIs set by regulators around the world. And, this level of sucralose consumption would not exceed the levels found to be safe both in animals and people. Intake studies and analyses also indicate that actual average intakes are well below the ADI. Occasional daily intakes in excess of usual intakes or in excess of ADI levels are not considered to be a safety concern, based on both chronic and acute toxicity tests (see **Acute Toxicity**, page 8).

**Environment** – Sucralose is safe for the environment, based on a full environmental impact study conducted as part of the regulatory approval process. This evaluation included studies in invertebrate and vertebrate aquatic species and algae and microorganisms.<sup>83</sup>

**Internet** – Only trusted sources of information should be used as a reference for responsible information. The manufacturers of SPLENDA® Products are a credible source of information (e.g., [www.SPLENDAtruth.com](http://www.SPLENDAtruth.com), [www.SPLENDA.com](http://www.SPLENDA.com)) as well as other sources such as the detailed FDA preamble (<http://www.cfsan.fda.gov/~lrd/frg80403.html>) discussion that accompanies publication of the regulations\* for sucralose.

\*<http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=d9c370a3a322d9e2df34d4f52fdc608a&rgn=div8&view=txt&node=21:3.0.1.1.3.9.1.20&idno=21> and <http://www.fda.gov/OHRMS/DOCKETS/98fr/081299b.pdf>

## CONCLUSIONS

Sucralose has undergone significant research, testing and scrutiny by the developing company, as well as noted scientific experts and regulatory agencies. The data demonstrate and the experts agree that sucralose is a safe no-calorie sweetener appropriate for all consumers and patients, including but not limited to adults, children, breastfeeding mothers, pregnant women, and patients with diabetes, with no restrictions due to medical reasons or otherwise.

Compared to other FDA-approved, no-calorie sweeteners, sucralose provides a unique combination of both a sugar-like taste without a bitter aftertaste, and good stability in foods and beverages, even with cooking and baking.

As such, sucralose, commercially available as SPLENDA® Brand Sweetener, is one additional easy-to-adopt tool to help reduce the calories from added sugar, which now represents a significant percentage of the average American's caloric intake. SPLENDA® Sweetener Products may be a useful adjunct to health management strategies both for controlling calories and added sugar intake.

## REFERENCES

1. Standards of medical care in diabetes – 2006. Position Statement – American Diabetes Association. *Diabetes Care*. 2006;29:S4-42.
2. Code of Federal Regulations: Title 21, Part 172. Available at: [http://www.access.gpo.gov/nara/cfr/waisidx\\_01/21cfrv3\\_01.html](http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfrv3_01.html). Accessed December 1, 2006.
3. Economic Research Service Loss-adjusted annual per capita food supply series, USDA. *Food Review*. 25:2-15,2003.
4. US Department of Agriculture. *Agriculture Fact Book: 2001-2002, Chapter 2: Profiling Food Consumption in America*. Available at: <http://www.usda.gov/factbook/chapter2.htm>. Accessed March 2, 2006.
5. US Department of Health and Human Services and Department of Agriculture. *Dietary guidelines for Americans: 2005*. January 12, 2005. Available at: <http://www.health.gov/dietaryguidelines/dga2005/document/>. Accessed December 1, 2006.
6. US Department of Health and Human Services, Centers for Disease Control and Prevention. *Overweight and obesity: Frequently asked questions (FAQs)*. Available at: <http://www.cdc.gov/nccdphp/dnpa/obesity/faq.htm#adults>. Accessed March 25, 2006.
7. World Health Organization. *Global strategy on diet, physical activity and health*. Available at: <http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/>. Accessed December 1, 2006.
8. National Institute of Diabetes and Digestive and Kidney Diseases. *Do you know the health risks of being overweight?* Available at: [http://www.win.niddk.nih.gov/publications/health\\_risks.htm](http://www.win.niddk.nih.gov/publications/health_risks.htm). Accessed March 25, 2006.
9. Allison DB, Zannolli R, Narayan KM. The direct health care costs of obesity in the United States. *Am J Public Health*. 1999;89:1194-1199. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=10432905&query\\_hl=25&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10432905&query_hl=25&itool=pubmed_DocSum). Accessed December 1, 2006.
10. Wolf AM, Colditz GA. Current estimates of the economic cost of obesity in the United States. *Obesity Research*. 1998;6:97-106. Available at: [http://www.obesityresearch.org/cgi/content/abstract/6/2/97?ijkey=a28ecad6cfbdadb1acbd76795d22bb58f4a65922&keytype2=tf\\_ipsecsha](http://www.obesityresearch.org/cgi/content/abstract/6/2/97?ijkey=a28ecad6cfbdadb1acbd76795d22bb58f4a65922&keytype2=tf_ipsecsha). Accessed December 1, 2006.
11. Wang G, Dietz WH. Economic burden of obesity in youths aged 6 to 17 years: 1979–1999 [electronic article]. *Pediatrics*. 2002;109:e81. Available at: <http://pediatrics.aappublications.org/cgi/content/full/109/5/e81>. Accessed March 28, 2006.
12. Fowler-Brown A, Kahwati LC. Prevention and treatment of overweight in children and adolescents. *American Fam Phys*. 2004;69:2591-2598. Available at: <http://www.aafp.org/afp/20040601/2591.html>. Accessed December 1, 2006.
13. Torgan C. Childhood obesity on the rise. In: Word on Health, NIH. Available at: <http://www.nih.gov/news/WordonHealth/jun2002/childhoodobesity.htm>. Accessed March 31, 2006.
14. Barlow SE, Trowbridge FL, Klish WJ, Dietz WH. Medical evaluation of overweight children and adolescents: reports from pediatricians, pediatric nurse practitioners, and registered dietitians. *Pediatrics*. 2002;110:222–228.
15. Styne DM. Childhood and adolescent obesity: prevalence and significance. *Pediatr Clin North Am*. 2001;84:823-854.
16. Hansen JR, Fulop MJ, Hunter, MK. Type 2 diabetes mellitus in youth: a growing challenge. *Clinical Diabetes*. 2000;18:52. Available at: <http://journal.diabetes.org/clinicaldiabetes/V18N22000/pg52.htm>. Accessed December 1, 2006.

17. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med*. 2002;346:802-810. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=11893791&query\\_hl=4&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11893791&query_hl=4&itool=pubmed_docsum). Accessed December 1, 2006.
18. Strauss RS. Childhood obesity and self-esteem [electronic article]. *Pediatrics*. 2000;105:e15. Available at: <http://pediatrics.aappublications.org/cgi/content/full/105/1/e15>. Accessed March 29, 2006.
19. Hesketh K, Wake M, Waters E. Body mass index and parent-reported self-esteem in elementary school children: evidence for a causal relationship. *International J Obesity*. 2004;28:1233-1237. Available at: <http://www.nature.com/ijo/journal/v28/n10/abs/o802624a.html;jsessionid=o63CD0A5BC1C93AB6AE47ECF500F6672>. Accessed December 1, 2006.
20. Food and Drug Administration. FDA approves new high-intensity sweetener sucralose. April 1, 1998. Talk Paper T98-16. Available at: <http://www.cfsan.fda.gov/~lrd/tpsucral.html>. Accessed December 1, 2006.
21. Health and Consumer Protection Directorate-General, European Commission. Opinion of the Scientific Committee on Food on sucralose. September 7, 2000. Available at: [http://europa.eu.int/comm/food/fs/sc/scf/out68\\_en.pdf](http://europa.eu.int/comm/food/fs/sc/scf/out68_en.pdf). Accessed December 1, 2006.
22. Sucralose Food Additive Petition 7A3987. September 2, 1987, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
23. Jenner MR. The uses and commercial development of sucralose. In: Grenby TH, ed. *Advances in Sweeteners*. Glasgow: Blackie Academic & Professional; 1996:253-262.
24. Wiet SG, Beyts PK. Sensory characteristics of sucralose and other high intensity sweeteners. *J Food Sci*. 1992;57:1014-1019.
25. Horne J, Lawless HT, Speirs W, Sposato D. Bitter taste of saccharin and acesulfame-K. *Chem Senses*. 2002;27:31-38. Available at: <http://chemse.oxfordjournals.org/cgi/reprint/27/1/31>. Accessed December 1, 2006.
26. Kuhn C, Bufe B, Winnig M, et al. Bitter taste receptors for saccharin and acesulfame K. *J Neuroscience*. 2004;24:10260-10265. Available at: <http://www.jneurosci.org/cgi/content/abstract/24/45/10260>. Accessed December 1, 2006.
27. Nie Y, Vignes S, Hobbs JR, Conn GL, Munger SD. Distinct contributions of T1R2 and T1R3 taste receptor subunits to the detection of sweet stimuli. *Curr Biol*. 2005;15:1948-1952.
28. International Food Information Council. Gestational diabetes and low-calorie sweeteners: Answers to common questions. February 2005. Available at: <http://www.ific.org/publications/brochures/gestdiabetes.cfm>. Accessed April 3, 2006.
29. Tso P. Gastrointestinal secretion, digestion, and absorption. In: Rhoades R and Tanner G, eds. *Medical Physiology*. 2nd ed. Lippincott Williams & Wilkins; 2003. Available at: <http://connection.lww.com/products/rhoades/documents/smch27.pdf>. Accessed December 1, 2006.
30. Sucralose Food Additive Petition 7A3987. February 9, 1987;2-3:275-890, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
31. Roberts A, Renwick AG, Sims J, Snodin DJ. Sucralose metabolism and pharmacokinetics in man. *Food Chem Tox*. 2000;38(S2):S31-S41.
32. Grice HC, Goldsmith LA. Sucralose: an overview of the toxicity data. *Food Chem Tox*. 2000;38(S2):S1-S6.
33. Sims J, Roberts A, Daniel JW, Renwick AG. The metabolic fate of sucralose in rats. *Food Chem Tox*. 2000;38(S2):S115-S121.
34. Anderson AD, Jain PK, Fleming S, Poon P, Mitchell CJ, MacFie J. Evaluation of a triple sugar test of colonic permeability in humans. *Acta Physiol Scand*. 2004;182:171-177. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=15450113&query\\_hl=6&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15450113&query_hl=6&itool=pubmed_docsum). Accessed December 1, 2006.

35. John BA, Wood SG, Hawkins DR. The pharmacokinetics and metabolism of sucralose in the mouse. *Food Chem Tox.* 2000;38(S2):S107-S110.
36. Wood SG, John BA, Hawkins DR. The pharmacokinetics and metabolism of sucralose in the dog. *Food Chem Tox.* 2000;38(S2):S99-S106.
37. John BA, Wood SG, Hawkins DR. The pharmacokinetics and metabolism of sucralose in the rabbit. *Food Chem Tox.* 2000;38(S2):S111-S113.
38. Sucralose Food Additive Petition 7A3987. February 9, 1987;10:2661-2698, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
39. Sucralose Food Additive Petition 7A3987. February 9, 1987;10:2754-2778, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
40. Mezitis NH, Maggio CA, Koch P, Quddoos A, Allison DB, Pi-Sunyer FX. Glycemic effect of a single high oral dose of the novel sweetener sucralose in patients with diabetes. *Diabetes Care.* 1996;19:1004-1005.
41. Grotz VL, Henry RR, McGill JB, et al. Lack of effect of sucralose on glucose homeostasis in subjects with type 2 diabetes. *J Am Diet Assoc.* 2003;103:1607-1612.
42. Sucralose Food Additive Petition 7A3987. August 16, 1996;1:1-357, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
43. Mandel ID, Grotz VL. Dental considerations in sucralose use. *J Clin Dent.* 2002;13:116-118.
44. Farhadi A, Keshavarian A, Holmes EW, Fields J, Zhang L, Banan A. Gas chromatographic method for detection of urinary sucralose: application to the assessment of intestinal permeability. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2003;784:145-154. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=12504193&query\\_hl=14&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12504193&query_hl=14&itool=pubmed_docsum). Accessed December 1, 2006.
45. McLean Baird I, Shephard NW, Merritt RJ, Hildick-Smith G. Repeated dose study of sucralose tolerance in human subjects. *Food Chem Tox.* 2000;38(S2):S123-S130.
46. Goldsmith LA. Acute and subchronic toxicity of sucralose. *Food Chem Tox.* 2000;38(S2):S53-S69.
47. Center for Food Safety and Applied Nutrition (CFSAN). Food and Drug Administration, HHS. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Search&itool=pubmed\\_AbstractPlus&term=%22Food+and+Drug+Administration%2C+HHS%22%5BCorporate+Author%5D](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Search&itool=pubmed_AbstractPlus&term=%22Food+and+Drug+Administration%2C+HHS%22%5BCorporate+Author%5D). Food Additives Permitted for Direct Addition to Food for Human Consumption; Sucralose. Final Rule. Fed Regist. javascript:AL\_get(this, 'jour', 'Fed Regist. '); 1998 April 3; 63(64):16417-16433.
48. Sucralose Food Additive Petition 7A3987. February 9, 1987;45:13389-13457, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
49. Sucralose Food Additive Petition 7A3987. December 6, 1988;A13:A2762-2865, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
50. Sclafani A, Clare RA. Female rats show a bimodal preference response to the artificial sweetener sucralose. *Chem Senses.* 2004;29:223-229. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=15269124&query\\_hl=12&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15269124&query_hl=12&itool=pubmed_docsum). Accessed December 1, 2006.
51. Mann SW, Yuschak MM, Amyes SJG, Aughton P, Finn JP. A combined chronic toxicity/carcinogenicity study of sucralose in Sprague-Dawley rats. *Food Chem Tox.* 2000;38(S2):S71-S89.
52. Sucralose Food Additive Petition 7A3987. December 6, 1988;A14:2866-3188, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
53. Sucralose Food Additive Petition 7A3987. March 23, 1994;1:22-470 and 2:471-738, A2762-2865, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
54. Flamm WG, Blackburn GL, Comer CP, Mayhew DA, Stargel WW. Long-term food consumption and body weight changes in neotame safety studies are consistent with the allometric relationship observed for other sweeteners and during dietary restrictions. *Regul Toxicol Pharmacol.* 2003;38:144-156.

55. Finn JP, Lord GH. Neurotoxicity studies on sucralose and its hydrolysis products with special reference to histopathologic and ultrastructural changes. *Food Chem Tox.* 2000;38(S2):S7-S17.
56. Sucralose Food Additive Petition 7A3987. February 9, 1987;14-15:4097-4280, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
57. Sucralose Food Additive Petition 7A3987. February 9, 1987;46:13477-13523, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
58. Sucralose Food Additive Petition 7A3987. March 29, 1994;1:72-509, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
59. Mann SW, Yuschak MM, Amyes SJG, Aughton P, Finn JP. A carcinogenicity study of sucralose in the CD-1 mouse. *Food Chem Tox.* 2000;38(S2):S91-S98.
60. Kille JW, Tesh JM, McAnulty PA, et al. *Food Chem Tox.* 2000;38(S2):S43-S52.
61. Kille JW, Ford WCL, McAnulty P, et al. Sucralose: lack of effects on sperm glycolysis and reproduction in the rat. *Food Chem Tox.* 2000;38(S2):S19-S29.
62. Rodearmel SJ, Grotz VL, Goldsmith LA, et al. Effectiveness of *Families on the Move!* A family-based approach for preventing excessive weight gain in children [abstract]. Pediatric Academic Societies Meeting, April 2006. Taken from: Hill JO, Personal Communication. Available at: <http://www.abstracts2view.com/pas/search.php?search=do&intMaxHits=10&where%5B%5D=&andnot%5B%5D=&query=Rodearmel>. Accessed December 1, 2006.
63. Suenart P, Bulteel V, Den Hond E, et al. In vivo influence of nicotine on human basal and NSAID-induced gut barrier function. *Scand J Gastroenterol.* 2003;38:399-408. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=12739712&query\\_hl=14&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12739712&query_hl=14&itool=pubmed_docsum). Accessed December 1, 2006.
64. Meddings JB. Review article: Intestinal permeability in Crohn's disease. *Aliment Pharmacol Ther.* 1997;11(S3):47-53. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=9467978&query\\_hl=14&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9467978&query_hl=14&itool=pubmed_docsum). Accessed December 1, 2006.
65. Brown GR, Lindberg G, Meddings J, Silva M, Beufler B, Thiele D. Tumor necrosis factor inhibitor ameliorates murine intestinal graft-versus-host disease. *Gastroenterology.* 1999;116(3):593-601. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=10029618&query\\_hl=14&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10029618&query_hl=14&itool=pubmed_docsum). Accessed December 1, 2006.
66. Smecul E, Bai JC, Sugai E, et al. Acute gastrointestinal permeability responses to different non-steroidal anti-inflammatory drugs. *Gut.* 2001;49:650-655. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=11600467&query\\_hl=14&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11600467&query_hl=14&itool=pubmed_docsum). Accessed December 1, 2006.
67. Sucralose Food Additive Petition 7A3987. March 7, 1997;6:1-83, on file: Center for Food Safety and Applied Nutrition (CFSAN), U.S. Food and Drug Administration.
68. Grotz VL, Little R. Lack of effect of sucralose on glucose or HbA1c monitoring [Draft manuscript]. Fort Washington, PA: McNeil Nutritionals, LLC.
69. Blackburn GL, Kanders BS, Lavin PT, Keller SD, Whatley J. The effect of aspartame as part of a multidisciplinary weight-control program on short- and long-term control of body weight. *Am J Clin Nutr.* 1997;65:409-418.
70. Berryman GH, Hazel GR, Taylor JD, Sander PG, Weinberg MS. A case of safety of cyclamate and cyclamate-saccharin combinations. *Am J Clin Nutr.* 1968;21:673-687.
71. Morris DH, Mance MJ, Bell KJ, Ward A. Weight loss and consumption of artificial sweeteners among overweight women and men [Abstract]. *J Am Dietetic Assoc.* 9. 1989;(suppl. A-94).
72. Rolls BJ. Effects of intense sweeteners on hunger, food intake, and body weight: a review. *Am J Clin Nutr.* 1991;53:872-878.

73. Porikos KP, Booth G, Van Itallie TB. Effect of covert nutritive dilution on the spontaneous intake of obese individuals: a pilot study. *Am J Clin Nutr.* 1977;30:1638-1644.
74. Porikos KP, Hesser MF, Van Itallie TB. Caloric regulation in normal weight men maintained on a palatable diet of conventional foods. *Physiol Behav.* 1982;29:293-300.
75. Porikos KP, Pi-Sunyer FX. Regulation of food intake in human obesity: studies with caloric dilution and exercise. *Clin. Endocrinol Metab.* 1984;13:547-561.
76. Porikos KP, Van Itallie TB. Efficacy of low-calorie sweeteners in reducing food intake: studies with aspartame. In: LJ Filer Jr., LD Stegink, eds. *Aspartame: Physiology and Biochemistry.* New York: Marcel Dekker, Inc.; 1984:273-286.
77. Gougeon R, Spidel M, Lee K, Field CJ. Canadian Diabetes Association National Nutrition Committee Technical Review: non-nutritive intense sweeteners in diabetes management. *Canadian J Diab.* 2004;28:385-399. Available at: <http://www.diabetes.ca/files/p.385-399.pdf>. Accessed December 1, 2006.
78. Sigman-Grant M, Hsieh G. Reported use of reduced sugars foods and beverages reflect high quality diets. *J Food Science.* 2004;70:S42-S46.
79. Raben A, Vasilaras TH, Moller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. *Am J Clin Nutr.* 2002;76:721-729.
80. Rodearmel SJ, Grotz VL, Goldsmith LA, et al. Effectiveness of *Families on the Move!* A family-based approach for preventing excessive weight gain in children [Abstract]. Pediatric Academic Societies Meeting, April 2006. Available at: <http://www.abstracts2view.com/pas/search.php?search=do&intMaxHits=10&where%5B%5D=&andnot%5B%5D=&query=Rodearmel>. Accessed December 1, 2006.
81. Center for Food Safety and Applied Nutrition (CFSAN). Food and Drug Administration, HHS. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Search&itool=pubmed\\_AbstractPlus&term=%22Food+and+Drug+Administration%2C+HHS%22%5BCorporate+Author%5D](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Search&itool=pubmed_AbstractPlus&term=%22Food+and+Drug+Administration%2C+HHS%22%5BCorporate+Author%5D). Food labeling: health claims; dietary noncariogenic carbohydrate sweeteners and dental caries. Final rule. Fed Regist. javascript:AL\_get(this, 'jour', 'Fed Regist. '); 2006 Mar 29;71(60):15559-64.
82. International Food Information Council, August 1996. Questions and answers about acceptable daily intake. Available at: <http://www.ific.org/publications/qa/adiqa.cfm>. Accessed April 3, 2006.
83. Center for Food Safety and Applied Nutrition (CFSAN). Food and Drug Administration, HHS. Available at: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Search&itool=pubmed\\_AbstractPlus&term=%22Food+and+Drug+Administration%2C+HHS%22%5BCorporate+Author%5D](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Search&itool=pubmed_AbstractPlus&term=%22Food+and+Drug+Administration%2C+HHS%22%5BCorporate+Author%5D). Food Additives Permitted for Direct Addition to Food for Human Consumption; Sucralose. Final Rule. Fed Regist. javascript:AL\_get(this, 'jour', 'Fed Regist. '); 1998 April 3;63(64):16431.



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