Abstract

Sucralose is an edulcorant obtained from sucrose where three hydroxylic groups, from positions 4, 1 and 6 are replaced by 3 chlorine atoms to form the compound 4,1′,6′ trichlorogalactosacarose. Sucralose is among the food additives with the code of E-955 and it is 600 times sweeter than sugar. It is a good alternative to maintain energy intake and body weight. Because sucralose is not absorbed to a large extent, and at the same time the received small amount is disposed of the body unchanged, and it is not used as an energy source, it does not form any other metabolites, and it does not cause bioaccumulation, it is safe for consumption. In studies of sucralose, it was determined that sucralose does not have carcinogenic, mutagenic and teratogenic effects.

Key Words: Sucralose, Sweetener, Cancer, Nutrition

Introduction

Obesity affects a lot of people all over the world (1). In Turkey, obesity is seen 30.3% of adults, and 34.6% of adults are slightly overweight (2). Among the most important factors causing obesity are changes in the diet-style, genetic factors, and lack of physical activity. Besides the increase in the daily intake of energy, the increase in the consumption of added sugars and monosaccharides causes an increase in the carbohydrate rate in a diet, and in turn, different metabolic changes have the risk for many metabolic diseases (1). Recently in the USA, 16-18% (≈300 kcal/day) of the energy adults take daily from their diet is met only by added sugars and monosaccharides (3). However, the World Health Organization (WHO) recommends that the daily energy intake from added sugars should be ≤10%, within the global strategy on diet, physical activity, and health (4). Moreover, American Heart Association (AHA) recommends that the daily consumption of added sugars for women and men should not be more than 100 and 150 kcal, respectively (5). According to the data by Turkey Nutrition and Health Survey, the consumption of sugars by adults is 28-35 g (112-140 kcal/day) and it is in line with recommendations (2). In order to limit/decrease energy intake without spoiling taste and to maintain diet quality, different solutions are focused. One of the
solutions that come to mind immediately is the sweeteners that do not contain energy and provide the same taste (6). With the use of sweeteners that do not increase or add less to diet energy, it is possible to reduce and control the risk of obesity and other diseases by maintaining bodyweight (7).

Sweeteners are classified into two groups as containing and not containing energy. The sweeteners that contain less energy compared to sugars are mannitol, sorbitol, xylitol, erythritol, d-tagatose, isomalt, lactulose, maltitol, isomaltulose, and trehalose. The sweeteners that do not contain energy are acesulfame K, aspartame, neotame, saccharine, stevia, and sucralose. American Diabetes Association (ADA) with the updates made in 2008 stated that sugar alcohols and sweeteners that do not contain energy are safe when they are consumed in-between the daily consumption levels determined by the Food and Drug Administration (FDA) (6).

Sucralose, which is popular for its low consumption rate, is obtained from sucrose where three hydroxylic groups, from positions 4, 1 and 6 are replaced by 3 chlorine atoms. It is chemically called “4,1’,6’ trichlorogalactosacarose, and it is also called as “1,6-dichloro-1,6-dideoxy-beta-D-fructofuranosyl-4-chloro-4-deoxy-alpha-D-galactopyranoside” and as “4,1’,6’-trichloro-4,1’,6’-trideoxi-galacto-sucrose”. Sucralose was discovered accidentally in 1976 by Shashikant Phadnis, a student who were seeking to synthesize halogenated sugars, he erroneously executed a task, chlorinating the sugar. In 1989, while the scientists Leslie Hough and Khan were evaluating the different effects of sweeteners derived from sucrose, it was found to be linked with determinate halogens (8).

Studies indicate the existence of 2 hydrolysis products of sucralose, 4-CG and 1,6-DCF, and that these products are more rapidly absorbed after oral administration than the original sucralose compound. The hydrolysis product 4-CG is excreted, essentially in intact form, in the urine, while 1,6-DCF follows one of two principal metabolic pathways: reduction to 1,6 dichloroaminitol, rapidly excreted in unaltered form in the urine, or conjugated with glutathione (8).

Sucralose is present among food supplements with the code of E-955 (9). Sucralose does not have the bitter aftertaste attributed to some other non-nutritive sweeteners (10), and it is resistant to mid-acidic environments and high temperatures (11). Because of its strongly stable Cl-carbon links, it is not digested and metabolized and separated into its metabolites (12, 13). It is not soluble in water, not acidogenic, or cariogenic (14). Also, sucralose does not interfere in the utilization and absorption of glucose, metabolism of carbohydrates and secretion of insulin. Therefore, it is a safe substance able to be ingested by diabetes patients (15). It is not bio-accumulative in water and fat masses in human body (14, 16). 85% of sucralose in not absorbed when orally consumed and is eliminated from the body without any changes via feces (11, 16, 19). No side effects have been observed in the digestive system when orally consumed in high doses. Because it is 600 times sweeter than sugar, although it is consumed in high doses, it is consumed in very low quantities (11). Even for people who consume it in very high doses, total assumed consumption dose is observed to be <3 mg/kg/day. Intake in low doses does not form substrate for the digestive system microbiota; that is, it does
not produce intestinal fermentation metabolites/products (16). In rodents, which consumed sucralose 100 times more than humans, no side effects were observed in the digestive system (11, 20, 22). Only 2-3% of sucralose is metabolized as glucuronide when orally consumed and the rest is eliminated via urine (18). It is a very important characteristic for a healthy life (11, 16, 19, 21). In the radio-isotopic studies, because of the ability of sucralose to dissolve in water, it was determined to move rapidly and reach all the tissues easily. In spite of this, it was found out that sucralose does not transport into baby via human milk and placenta, and into central nervous system (11, 16).

Sucralose strongly connects to the carbons of Cl atoms and therefore, it was observed that it is not used as an energy source in humans and in animals (11, 16, 19). Glucuronic metabolites and sucralose do not affect cytochrome P450 secretion (23). In the radio-isotopic studies, it was determined that sucralose and its metabolites do not link to proteins (18).

Its peak period in the plasma is 1.5-3 hours and its half-life is 13 hours (18). In its application for thirteen weeks with a dose of 1, 3, 7 mg/kg/day, it is seen that the plasma sucralose concentrations do not increase in the 3rd, 4th, and 6th weeks (21).

Moreover, because of its stability in wide pH variations, it can maintain its stability up to one year in non-alcoholic beverages (13). For its thermic characteristics and because it does not interact with other nutritional elements, sucralose has been allowed to be used in about 15 foods and beverages (24, 25). Then, in 1999, its use became widespread in all foods, traditional beverages, and cooked or baked foods (26, 28). Its powdery form started to be used in products such as powdery beverages, flavorings, starters, ready sauces, bread and cereals, milk deserts, cooked vegetables, pasteurized products (15). In many countries, it is used in more than 300 products, for example in Brazil it is used in more than 500 products (29). Its commercial form, Splenda, was produced by McNeil Nutritionalist (LLC McNeil) and its use became more widespread. Because sucralose is 600 times sweeter than sugar, it quantity for use is very small. For this reason, maltodextrin has been added to provide mass and structure for an easier use. Splenda’s dry weight is 1% sucralose and 99% maltodextrin (27, 28). As it is known, maltodextrin is approved to be used safely (Generally Recognized as Safe - GRAS) by FDA, it is a digestible and non-toxic starch based carbohydrate product (30). Because of the all mentioned characteristics of sucralose, its use is stated to be safe.

The first studies about the safety of sucralose in humans are by FDA Red Book (1982) and Organization for Economic Co-operation and Development (OECD) (1981, 1983, 1984); sucralose was among the many nutritious substances studied in order to be internationally standardized for safe production and consumption. It was approved as a food additive by the Joint Expert Committee on Food Additives (JECFA) in 1989. Two years later, in Canada (Canada’s Department of Health and Welfare - Canada Gazette), it was accepted to be safe and allowed to be used. Later on, in 1998, FDA carried out its biggest research program on determining the usage characteristics of food additives, covering 110 studies with humans and animals. These studies were on points such as determining chemical structure,
mutagenic and clastogenic potential, short-term genetic toxicity, metabolic and pharmacokinetic characteristics for human-rodent-rat-dog-rabbit-etc., acute and short term toxicity, high dose acute intake and long-term consumption toxicity, sub-chronic toxicity to evaluate regular daily intake, energy potential, immunotoxic and neurotoxic potential, connection with the cytochrome P450 enzyme, reproduction, toxicity based on life-time chronic consumption, human tolerance status for repetitive and assumed maximum consumption, carbohydrate regulation and metabolic links, insulin secretion in diabetic and healthy people, glucose homeostasis, long-term glucose control, effects on caries, bacteria production and control on teeth. After these studies, sucralose was approved to be safe by FDA; and in 1999, it was accepted in Japan (Japan’s Department of Health and Welfare-JMHW). Critical safety studies were published in early 2000s. Its use in Europe was approved by European Union’s Scientific Committee on Food (SCF) in 2000; and in 2004, it was added among sweeteners in the European Union directives. Approved by sixteen countries, experts of genetics, toxicology, oncology, general toxicology, clinical toxicology, immunology, physiology, dietary, neurology, reproductive and developmental toxicology, biochemistry, pharmacokinetics and metabolism, who were not assigned by government agencies, formed the Mc Neil Nutritionalist Panel and determined that sucralose is safe for general use (30).

The acute, sub-chronic, and chronic exposure studies of sucralose to determine its carcinogenic potential was realized by Goldsmith (31). In the acute toxicity study, after applying 16 g/kg and 10 g/kg sucralose to mice and rats for 14 days, nothing was observed such as death, illness signs, or difference in body weights. Similar results were observed in the sub-chronic toxicity studies with rats, which consumed 0%, 1%, 2.5%, and 5% sucralose in their diets in 0, 10,000, 25,000 and 50,000 ppm concentrations, respectively. However, in rats which consumed 5% sucralose in their diets for 4 more weeks, apparent body weight loss and side effects were detected (p<0.01). Because sucralose is 600 times sweeter than sugar, with a lesser consumption, in sucralose gavage forms 0, 750, 1500, and 2500 mg/kg/day, nothing was observed such as clinical toxicity, death, and behavioral changes. In the group with the highest sucralose consumption rate, an apparent decrease in their food consumption and body weight was observed, and their full caecum weights were determined to be high. Besides these studies, in another study of sucralose to determine its carcinogenic effect, dogs had 0% (control group), 0.3%, 1.0%, and 3.0% sucralose for 12 months, with a dose of 89, 274, 858 mg/kg/day, in the diets and no harmful effects were observed. Diets containing >2.5% sucralose, that is 1865-3218 mg/kg/day, in rats were not fatal in sub-chronic studies. In another study on dogs, 900 mg/kg/day sucralose, a very high dose, was applied and it was observed to be safe (31).

In order to observe the long-term effects of sucralose, rats consumed 30000 ppm, 10,000 ppm, 30,000 ppm sucralose, that is 0.3%, 1.0%, 3.0%, respectively, for 104 weeks. For the first 14 weeks, no relationships were determined between sucralose consumption and longevity. No effects were observed on clinical status and behaviors. Yet the change in their body
weights was significant; the group with 30,000 ppm sucralose consumption, low body weight was observed. It was stated that tumor formation, benign or malignant neoplasm and changes in tissues and organs were not detected (32). Mann et al (33) remade this study with Sprague Dawley rats, another kind, and found no relationship between sucralose consumption and longevity, and they found no carcinogenic effects (33). As a result, sucralose consumption with a high dose does not have mutagenic, teratogenic, and carcinogenic effects (11). In addition, in another study, the acute genotoxic effects of sucralose on animals’ bone marrows and humans’ lymphocytes were evaluated. It was found out that sucralose do not affect the genes in these cells and was not harmful for the DNA. This result shows that sucralose is not bioactive, do not metabolize to reactive products, and do not cause bio-accumulation (34).

In order to observe the effects of sucralose on fetus, 14 carbon (C) signed sucralose was given to pregnant rats and rabbits. On the 6th and 15th days of the rats’ pregnancy, 500, 1000, 2000 mg/kg/day sucralose containing water; on the 6th and 19th days of the rabbits’ pregnancy, 175, 350, 750 mg/kg/day sucralose containing water was given. No teratogenic pathologic findings were observed (35).

The carcinogenic and toxicological studies of sucralose have generally made on animals, studies on humans is inadequate. In an human tolerance study of repetitive sucralose doses, 1.0, 2.5, 5.0 and 10.0 mg/kg/day sucralose with 48 hours intervals was consumed; later, 2.0 mg/kg/day and 5.0 mg/kg/day sucralose with 3 days intervals was consumed. No statistically significant difference was observed between the serum biochemical and hematologic, electrocardiogram, and urinary follow-up analyses (p>0.05) (36). Mclean Baird et. al (36) gave, in their randomized controlled single blind study on 118 healthy humans, 125 mg/day, 250 mg/day, and 500 mg/day sucralose, respectively, in each week for 3 weeks. No significant findings were observed in the analyses (p>0.05).

In a 12-week study of granule Splenda, the commercial form of sucralose, with a small sample, rats were given 0, 100, 300, 500, 1000 mg/day Splenda. The results of the evaluation tests show that Splenda decreased useful microbiota, caused histopathological changes in the colon by increasing the fecal pH, and increased body weight, P glycoprotein (P-gp), cytochrome P450 3A4 and 2D1 expression (37). This study had a very huge reflection and experts formed a panel to evaluate these negative results. Many parameters like the consumed diet, rats, their body weights, and feces analyses were thought to be inadequately controlled, and it was announced that there were significant inadequacies in the methodology and design of this study and that the results of this study were controversial (38).

The daily intake level of sucralose is determined as 5 mg/kg and assumed daily intake level as 0.1-2.0 mg/kg (6). The preference of sucralose instead of sugar and the assumed consumption rate among adults is 1.3 mg/kg on average, and the maximum consumption is 2.4 mg/kg (24, 39). The consumption of about 100 times more sucralose than these mentioned quantities in determined to be safe (40). Health authorities states that the consumption of all sweeteners that do not contain energy is safe.
in long-term unless the average intake levels are exceeded (40, 41).

**Conclusion and Recommendations**

In conclusion, sucralose is not used for energy and it is used in small quantities. It is eliminated from the body without being absorbed to a large extent and without changing. It does not form other metabolites and does not cause bio-accumulation in body. In short, it is determined that sucralose does not have carcinogenic, mutagenic and teratogenic effects and thus, can be safely consumed. Sucralose is a safe and healthy alternative instead of sugar for it limits energy intake and helps maintain body weight. Therefore, by consuming sucralose, obesity and the risk for cancer may be diminished, and a healthy life may be realized.

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**References**

30. Grotz VL, Munro IC. An overview of the safety of sucralose. Regulatory
Tevfikolu L. and Akbulut G.  

40. FSAI (Food Safety Authority of Ireland). A Surveillance Study of the Sweetener Sucralose (E 955) in Irish Retail Products 2005.  