



## An overview of the safety of sucralose

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### ABSTRACT

Sucralose is a non-nutritive sweetener used in a broad range of foods and beverages and is the non-nutritive sweetener in retail SPLENDA<sup>®</sup> Sweetening Products, composed of sucralose and common food ingredients. A review of the extensive body of evidence that supports the safety of sucralose is provided. The results of an independent review of a new study investigating the safety of a sucralose-mixture retail product, Granulated SPLENDA<sup>®</sup> No Calorie Sweetener, are also discussed. The collective evidence supports the conclusion that the ingredient, sucralose, is safe for use in food and that the sucralose-mixture product, Granulated SPLENDA<sup>®</sup> No Calorie Sweetener, is also safe for its intended use.

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### 1. Introduction

Sweet taste is a natural preference in humans (Beidler, 1982; Lawless, 1985). In the U.S., the average adult consumes over 300 calories per day in added sugars (USDA, 2001–2, 2003). Excess calorie consumption is a significant concern, due to its correlation with obesity. Although the causes of obesity are multifactorial (Grundy, 1998; Kaila and Raman, 2008), non-nutritive sweeteners represent one way for consumers to decrease calorie intake by reducing calorie intake from sugar. Research shows that non-nutritive sweeteners can be used to achieve overall caloric reduction and help manage body weight (Rolls, 1991; Blackburn et al., 1997; de la Hunty et al., 2006; Rodearmel et al., 2007).

Sucralose, a substituted disaccharide (Merck, 2006), is a non-nutritive sweetener that is synthesized by selective chlorination of sucrose at three of the primary hydroxyl groups, involving inversion of configuration at carbon-4, from the gluco- to the galacto-analogue. As a non-nutritive sweetener, sucralose has qualities of specific interest to food and beverage manufacturers, as well as to consumers. Sensory studies show that sucralose does not have the bitter aftertaste attributed to some other non-nutritive sweeteners (Wiet and Beyts, 1992; Horne et al., 2002; Kuhn et al., 2004). Sucralose is also highly stable at elevated temperatures that are often used in food, beverage and drug manufacturing processes, so that product sweetness levels can be maintained following cook-

ing, baking and/or pasteurization. Sucralose also has excellent stability in low-pH products, so that sweetness degradation is not a determining factor in the shelf-life of such products. Although sucralose has become a popular sweetener, estimated daily intakes are low. This is because, like other non-nutritive sweeteners, sucralose is intensely sweet. By weight, sucralose is about 600 times sweeter than sucrose (Wiet and Beyts, 1992; Grice and Goldsmith, 2000).

McNeil Nutritionals, LLC (McNeil), a Johnson & Johnson company, markets retail SPLENDA<sup>®</sup> Sweetener Products, which contain the non-nutritive sweetener, sucralose, and common food ingredients that add volume and texture. For example, by dry weight, Granulated SPLENDA<sup>®</sup> No Calorie Sweetener is approximately 1% sucralose and 99% maltodextrin.

Maltodextrin is a starch-based carbohydrate that is completely digested and non-toxic. The safety of maltodextrin for human consumption has been affirmed by the United States Food and Drug Administration (FDA). Maltodextrin is affirmed as Generally Recognized as Safe (GRAS) for general use in foods by the FDA under Title 21 of the Code of Federal Regulations, Part 184, Section 1444 (21 CFR §184.1444).

Similarly, sucralose has been found safe by public health authorities worldwide, on the basis of critical reviews of extensive safety research (JECFA, 1989, 1991; Canada Gazette, 1991; US FDA, 1998a, 1999; JMHV, 1999; SCF, 2000; EU, 2004; FSANZ, 2008 [formerly ANFSC, approved 1993]).

While there is a wide body of evidence supporting the safety of sucralose and other common food ingredients like maltodextrin,

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which enable consumer use of non-nutritive sweeteners, a recent study reported that a sucralose-mixture product containing maltodextrin (Granulated SPLENDA® No Calorie Sweetener), causes adverse effects in male rats consisting of alterations in body weight, gut microflora and changes in gut enzyme and protein activity (Abou-Donia et al., 2008). The authors indicate that the reported effects are related to the consumption of sucralose. At the request of McNeil, a panel of internationally recognized experts thoroughly reviewed the study design, results and conclusions. The panel found that the study had serious design flaws and did not represent evidence of any adverse health effect of either sucralose or the retail sucralose-mixture product tested (Brusick et al., submitted for publication). Given the broad use of sucralose and its clinical utility in calorie and carbohydrate management, it is important to convey such results, as well as a general understanding of the safety of sucralose to members of both the lay public and the scientific, including healthcare professional, community. The current paper briefly reviews the safety of sucralose and considers the safety of sucralose-mixture products, like Granulated SPLENDA® No Calorie Sweetener.

## 2. Review of safety research on sucralose

The safety of sucralose has been the subject of rigorous and extensive investigation. Consistent with regulatory requirements, the core sucralose safety research studies were designed and conducted in accordance with internationally recognized standards for such studies; e.g., FDA Redbook and OECD (OECD, 1981, 1983, 1984; US FDA, 1982). The critical safety studies are available in the published literature (Finn and Lord, 2000; Goldsmith, 2000; Grice and Goldsmith, 2000; John et al., 2000a,b; Kille et al., 2000a,b; Mann et al., 2000a,b; McLean Baird et al., 2000; Roberts et al., 2000; Sims et al., 2000; Wood et al., 2000). The entire sucralose safety research program is also the subject of the Sucralose Food Additive Petition that was submitted to, and reviewed by FDA (US FDA, 1998a, 1999). It represents one of the largest research programs ever conducted to investigate the safety of a new food additive. Over 110 studies (US FDA, 1998b) were included in the Sucralose Food Additive Petition, which was compiled by McNeil, consistent with the 1958 Food Additives Amendment that places on the manufacturer the responsibility of establishing safety through reliable scientific research and other information (21 CFR §170 and §171). This spectrum of studies is an intentional, carefully-designed and methodically-conducted, program to evaluate sucralose for potential safety concerns. Studies conducted included, but were not limited to:

- Physicochemical studies to assess the general chemical nature of sucralose.
- A wide range of short-term tests for genetic toxicity; to consider both mutagenic and clastogenic potential.
- Metabolism and pharmacokinetic studies in five species, including humans, confirming rodents and dogs as good surrogates for humans in safety assessments.
- Acute and short-term toxicity tests to assess effects of acutely high doses and establish high-dose levels for long-term evaluations.
- Subchronic toxicity tests in several species for preliminary assessment of safety with daily repeated exposure.
- Studies to confirm that sucralose is non-nutritive; i.e., not used by the body for energy.
- Tests for potential metabolic interaction with carbohydrate regulation.
- Specialized studies to assess immunotoxicity and neurotoxicity potential.

- Studies to assess the likelihood for interaction with or induction of cytochrome P450 enzymes.
- Reproduction and developmental studies, including a high-dose 2-generation study in rodents, an appropriate surrogate species, to assess the potential for effects on mating and fertility, and fetal health, growth and development – the latter including examination of all soft tissue and skeletal indices to evaluate the potential for birth defect induction of any type.
- Chronic (essentially lifetime) toxicity and carcinogenicity studies in appropriate animal models to assess long-term safety at levels far in excess of estimated human exposure.
- Human tolerance studies to confirm safety of repeated daily intakes well in excess of maximum estimated daily intakes.
- Studies in people with diabetes and in normoglycemic individuals to evaluate the potential to affect insulin sensitivity or glucose homeostasis, including longer-term glucose control.
- Bacterial, animal-model and human studies to investigate the potential to induce dental caries or otherwise support the growth of bacteria involved in dental caries.

Also submitted for review was other information important to deliberations on safety. This included, for example, rigorous stability studies to evaluate shelf-life and the fate of the new food additive under the proposed conditions of use, and exposure information from which experts can reliably estimate exposure with both acute intakes and average cumulative intakes over time, from the very young to the aged, and with ordinary and high-end use levels. Environmental studies were also submitted in the US and Europe to demonstrate the safety of sucralose in the environment.

Safety experts at the FDA, including toxicologists, risk assessment specialists, chemists and other scientists, critically evaluated all this information as part of their responsibility to protect the public health. In the U.S., “new food additives are presumed to be unsafe for their intended uses unless and until they are proven ‘safe’ on the basis of scientific data and information” (Rulis and Levitt, 2009). There is no provision in the Food, Drug and Cosmetic Act (FD&C Act) which permits FDA to consider potential benefits of a food additive as a weighting factor when considering the evidence to permit use, i.e., there is no “risk/benefit” analysis determined as there is with drugs. Rather, the FD&C Act directs FDA to base its decision-making for ruling solely on the assessment of whether the food additive has been proven safe for its intended use, which, by law, is defined as “reasonable *certainty* (emphasis added) of no harm” (Rulis and Levitt, 2009).

Other regulatory and health agencies have similar rigorous standards when determining the permissibility of a new food additive for use in the food supply. In all cases, rulings are made only following a thorough safety assessment of the collective body of relevant information, independent of the safety assessment made by the manufacturer or petitioner. Regulatory food safety agencies and other health authorities, such as the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) (JECFA, 1989, 1991), also look to internationally accepted norms for best practices in safety assessment research to guide their deliberations and are obligated to have appropriate scientific expertise applied in their evaluation of the available data.

As a result of critical reviews of all the available data, sucralose has been found safe for its intended use by public health authorities worldwide, including, for example, JECFA, (JECFA, 1989, 1991); the United States’ FDA (US FDA, 1998a, 1999); Japan’s Ministry of Health and Welfare (JMHW, 1999), the European Union’s Scientific Committee on Food (SCF, 2000; EU, 2004); Canada’s Department of Health and Welfare (Canada Gazette, 1991); and Food Standards Australia and New Zealand (FSANZ, 2008 [formerly

ANFSC, approved 1993]). Specifically, “FDA’s approval is based on the finding that sucralose is safe for human consumption” (US FDA, 1998b).

This same conclusion was also reached by an independent panel of 16 internationally recognized, non-governmental experts, requested by McNeil to assess the safety of sucralose, prior to its compilation of the Sucralose Food Additive Petition. This separate evaluation was conducted as a part of McNeil’s due diligence as a manufacturer to fully evaluate the safety research. The members of the panel – experts in genetic toxicology, oncology (carcinogenicity), acute and long term safety (general toxicology), clinical toxicology, immunology, neurology, pediatrics and reproductive and developmental toxicology, physiology, nutrition, biochemistry, pharmacokinetics and metabolism – concluded that sucralose is safe for its intended use.

### 3. Key points in sucralose safety

#### 3.1. Physicochemical properties and pharmacokinetics

The safety of sucralose may be anticipated by its molecular structure and physicochemical properties. Sucralose has a disaccharide base with chlorine substitutions for 3 hydroxyl groups. As such, like sucrose and other disaccharides, it is a relatively small molecule ( $M_w \sim 400$ ) and is polyhydroxylated, so that it is understandably highly water-soluble, not lipophilic, and not expected to be bioaccumulative. Metabolism studies using radiolabeled sucralose confirm that sucralose does not bioaccumulate (McLean Baird et al., 2000; Sims et al., 2000), consistent with its relative chemical preference for polar (e.g., water) vs. non-polar (e.g., fat) stores. Following consumption, most sucralose (approximately 85%) is not absorbed, and is eliminated unchanged in the feces (Grice and Goldsmith, 2000; John et al., 2000a; Roberts et al., 2000; Sims et al., 2000; Wood et al., 2000). In humans, no gastrointestinal (GIT) side effects would be expected with this large proportion of an oral dose being unabsorbed. While the proportion is large, actual amounts of unabsorbed sucralose are small, due to the very high sweetening potency of sucralose. Even for consumers considered “heavy users,” total estimated daily intake is less than 3 mg/kg/day. Thus, osmotic effects that could be associated with unabsorbed material in the GIT, if any, would be expected to be of no clinical consequence. In addition to low intakes, sucralose has been shown not to be a substrate for GIT microflora (Sims et al., 2000). The GIT is therefore not exposed to the types of lower intestinal fermentation byproducts (e.g., gas) associated with GIT symptoms that are sometimes found with fermentation of some poorly absorbed nutritive sweeteners. Separately, sucralose use has not been associated with gastrointestinal side effects in lifetime rodent feeding studies where intakes were thousands of times greater than estimated average human daily intakes (Grice and Goldsmith, 2000; Mann et al., 2000a,b). Similarly, with repeated daily dosing in clinical trials, sucralose was not found to produce any adverse events (McLean Baird et al., 2000; Grotz et al., 2003). The collective data indicate that there are no adverse gastrointestinal effects with the use of sucralose.

Of the small amount of sucralose that is absorbed following consumption (approximately 15% of an oral intake), most is also excreted unchanged. About 2–3% of an oral intake undergoes common phase II metabolism, specifically, glucuronidation (Roberts et al., 2000). Both unchanged sucralose and its glucuronide conjugates are excreted in urine, and readily eliminated with no bioaccumulation (Grice and Goldsmith, 2000; John et al., 2000a; McLean Baird et al., 2000; Roberts et al., 2000; Sims et al., 2000; Wood et al., 2000). Radiolabel studies confirm that absorbed sucralose is distributed to essentially all tissues, indicating incorpora-

tion into total body water, consistent with its highly water-soluble nature. While sucralose moves readily with body water, there is no active transport into milk, transplacentally, or across the blood-brain barrier into the central nervous system (Grice and Goldsmith, 2000; Sims et al., 2000).

Neither humans nor the relevant laboratory animal models studied use sucralose as a source of energy. It is not dechlorinated, and there is no evidence of degradation to any smaller chlorinated compounds (Grice and Goldsmith, 2000; John et al., 2000a; Roberts et al., 2000; Sims et al., 2000; Wood et al., 2000). Cytochrome P450 (CYP450) enzyme induction was explored (Hawkins et al., 1989), and tests indicate no likelihood of such an effect. This is consistent with the fact that the minor and only metabolic products of sucralose are glucuronide products and not products of metabolism by CYP450 enzymes.

Radiolabel studies also indicate no evidence of any protein binding or formation of any products other than the small amount of glucuronidation products. The half-life of all sucralose consumed and absorbed is relatively rapid  $\sim 13$  h, with peak plasma levels achieved in 1.5–3 h (Roberts et al., 2000). 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 (McLean Baird et al., 2000). The doses tested range from approximately the estimated average daily intake to approximately triple the maximum estimated daily intake.

Thus, an oral intake of sucralose is largely unabsorbed, excreted largely unchanged, is not metabolized as a source of energy or otherwise broken down to yield smaller chlorinated compounds, is not involved in the formation of any known haptens, is not bioaccumulated, and therefore appears essentially inert in the body. On the basis of its metabolic, pharmacokinetic and physicochemical properties, alone, relative safety could be expected.

#### 3.2. Acute exposure

Acute toxicity was assessed in studies conducted in rodents treated by gavage, allowing for extremely high doses of sucralose to be administered. These studies showed no adverse effect of sucralose in rats or mice at the highest doses tested, approximately 10–16 g/kg body weight (Goldsmith, 2000). This amount of sucralose is equivalent in sweetness to about 13 lbs of sugar/kg body weight, or 1000 lb of sugar-sweetness, for a 175-lb adult. For a child of 40 lb, this amount is equivalent in sweetness to about 240 lb 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.

#### 3.3. Long-term safety

Studies conducted show that sucralose is safe for use during pregnancy and from conception and throughout the lifetime (Mann et al., 2000a,b). 78-Week and 104-week studies in rats, both including an in utero phase, and a 104-week study in mice resulted in no evidence of toxicity or increased incidence, type or onset of tumors with intakes hundreds of times greater than maximum estimated human exposure (Mann et al., 2000a,b). The absence of toxicity was anticipated from subchronic studies (Goldsmith, 2000) and the pharmacokinetics and physicochemical properties of sucralose. The absence of carcinogenicity is consistent with the lack of genotoxicity found in a wide range of studies conducted to evaluate this potential (Grice and Goldsmith, 2000; Grotz et al., 2009). The amounts found safe in these essentially lifetime studies were, for the average-weight adult, equivalent in sweetness to more than 40 lb of sugar per day over the lifetime. Similarly, no birth defects are associated with sucralose use. The potential for teratogenic, mating and/or fertility effects was specifically studied

in rats whose only dietary source was standard rat chow incorporating sucralose at up to 3% of the dietary weight (Mann et al., 2000a; Kille et al., 2000a,b), which corresponded to an average daily intake of up to 1500 mg/kg body weight/day. For the average-weight adult, this is equivalent in sweetness to over 100 lb of sugar per day. Teratology studies in rabbits also showed sucralose not to be teratogenic (Kille et al., 2000b).

### 3.4. Clinical studies

Studies were conducted in humans to allow interpretation of the pharmacokinetic and metabolic relevance of the laboratory animal models used. These studies show that the rat, mouse and dog handle sucralose similarly to man. Rat studies are internationally considered by experts to be good physiological surrogates for man for assessing long-term safety. Human tolerance studies were also conducted. For example, in a randomized, double-blind, placebo-controlled 13-week study, subjects consumed sucralose daily at dosages of 125 mg for 3 weeks, followed by 250 mg daily for 4 weeks, and then 500 mg daily for 5 weeks. There were no adverse clinical effects noted in blood chemistry, hematology, urinalysis, or electrocardiogram parameters (McLean Baird et al., 2000). Sucralose was similarly well-tolerated in clinical studies designed to assess the potential for effects on insulin sensitivity and/or glucose control, both in normoglycemic and diabetic subjects (Sucralose Food Additive Petition, 1996; Grotz et al., 2003). Sucralose intakes in these studies were up to 1000 mg/person/day for up to 6 months. Sucralose did not produce any adverse events. Human studies also show that sucralose has no potential to induce dental caries (Steinberg et al., 1995, 1996; Meyerowitz et al., 1996; Mandel and Grotz, 2002) or affect glycemic control (Mezitis et al., 1996; Grotz et al., 2003). A recent study showed that SPLENDA® products, when incorporated into a lifestyle change program targeted to decrease sugar intake and increase physical activity with an aim of an overall –200 kcal/day energy expenditure, can be helpful in weight management in overweight children (Rodearmel et al., 2007).

### 3.5. Estimated daily intake

Estimated daily intakes are based on conservative assumptions, assuming aggressive replacement of sugar and predicted approximately 1.3 mg/kg body weight/day for the average adult and maximal intakes of up to 2.4 mg/kg body weight/day (US FDA, 1998a, 1999). Sucralose has been found safe at levels hundreds of times this amount. Pre-approval and post-marketing intake assessments also indicate that consumption levels of all non-nutritive sweeteners are well below long-term intake averages denoted as safe by regulators (FSAI, 2005; Renwick, 2006).

### 3.6. Sucralose mixtures

Sucralose has specifically been found safe for use in foods by food safety and health authorities around the world. FDA permits sucralose use as a general purpose sweetener (US FDA, 1999), based not only on studies designed to directly test the safety of sucralose, but also on food prototype studies and food chemistry studies. Sucralose is stable in vivo and remarkably stable in wide ranges of foods and food preparation processes. Breakdown products are possible through hydrolysis of sucralose to its two monosaccharide-like moieties, under certain conditions, particularly conditions of prolonged exposure to high acidity, however, total exposure estimated from foods is extremely low – approximately 7 µg/kg/bw day, – and the no-effect level established through rigorous safety assessment, including such studies as a 2-generation reproductive study and a 104-week carcinogenicity study in rats, was 30,000 µg/kg/day (US FDA, 1998a,b, 1999). Food chemistry

studies show no interactions stemming from sucralose that would indicate any need for further safety analysis. A small study in rats investigated the safety of the sucralose-mixture product, Granulated SPLENDA® No Calorie Sweetener, and reported increased body weight and alterations in gut microflora and gut enzyme and protein activity (Abou-Donia et al., 2008). Evaluation of this study, however, by a panel of internationally recognized experts in fields such as general toxicology, food and chemical safety, risk assessment, in vitro and in situ toxicology, toxicology study methodology and design, histopathology, nutrition, weight management, clinical practice and research found that the study had serious methodological and study design flaws, and that the data did not support the reported conclusions (Brusick et al., submitted for publication). The panel further concluded that the study presents no evidence of any adverse effect from either sucralose or SPLENDA® No Calorie Sweetener. The absence of evidence of any adverse effect is consistent with the known safety of both sucralose and maltodextrin, the sole ingredients in the product tested. While not designed as a safety assessment study, a recent clinical study of the utility of SPLENDA® No Calorie Sweetener in a program designed to help decrease calorie intake from sugar, reported no adverse effects (Rodearmel et al., 2007).

## 4. Overall conclusions

There exists an extensive database in both relevant animal models and humans, which is an appropriate basis for determining the safety of sucralose. Trained safety and health protection experts from around the world conclude from this database that sucralose is a safe food ingredient that can be safely consumed for a lifetime. FDA has specifically noted that it has found sucralose safe for use by children, and people with diabetes, and has found it to be safe for use in foods, generally. There are no limitations for use by any population subtypes (US FDA, 1998a, 1999). There is also no expectation, or evidence, of any interference of sucralose with health treatment regimens. Sucralose has also been found to have no effect on weight, although it can be utilized in weight management programs designed to help manage weight by reducing calorie intake from sugar. Both sucralose and the retail product, SPLENDA® No Calorie Sweetener, can be safely used and may be a useful adjunct to the diet in meal plans designed to reduce unwanted calories or carbohydrate from nutritive sweeteners.

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