Replacing Sugar with Sweeteners: Are Stevia, Aspartame, and Sucralose Linked to Rising Cancer Risks?

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Abstract

The increase in added sugar intake across the globe has become a serious health concern since it has a close correlation to obesity, type 2 diabetes, as well as cardiovascular disease. Sugar substitutes are commonly employed because they can facilitate calorie reduction, weight management, and glycemic control, especially in diabetics and people with metabolic syndromes. Increased use of sugar substitutes has led to concerns and speculations about artificial sweetener safety, particularly regarding potential carcinogenic activity, thus raising confusion and concern among both consumers and healthcare providers.

Stevia, Aspartame, and Sucralose, have become the most used sweeteners worldwide. However, though the World Health Organization, the Food and Drug Administration, as well as the European Food Safety Authority, accept their use as sweeteners, there are studies that conflict with this recommendation.

To reach a conclusive answer, a global data comparison assessed Stevia, Aspartame, and Sucralose's impact on the development of cancer. This paper analyzes various epidemiological studies, animal studies, proposed mechanisms, as well as global safety assessments including these conflicting studies. The literature review critically analyzes what degree of consistency or strength any conclusions hold, including any ironies between correlation or cause in any pre-existing studies.

The goal is to explore the extent to which Stevia, Aspartame, and Sucralose present a real risk of cancer. The reader will benefit from an objective, evidence-driven summary of the findings to demystify prevailing myths and pinpoint the areas in which further research is warranted.

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Introduction

An excessive increase of added sugar in diets has become a global health concern, contributing significantly to growing rates of obesity, type 2 diabetes, and a variety of cardiovascular disorders (“Get the Facts”). Added sugars are not naturally occurring. Instead, they are put into food or drinks, such as desserts or sodas, during processing and are promoted for weight-loss management or decreased sugar intake (“Get the Facts”). To fight these problematic health issues, national health organizations have published guidelines intended to reduce sugar intake. According to the American Heart Association (AHA), women should consume no more than 25 grams (6 teaspoons) of added sugars per day, while men should consume no more than 36 grams (9 teaspoons). Yet many Americans exceed these recommendations (“Added Sugars”).

To reduce sugar intake while maintaining sweetness in foods and beverages, both manufacturers and consumers have turned to sugar substitutes. In the late 1800s, this shift began with the accidental discovery of saccharin, and since then, the market has developed to include low- and zero-calorie sweeteners. Among the most commonly used today are Stevia, a natural sweetener derived from the leaves of the Stevia rebaudiana plant (Petruzzello); Aspartame, an artificial sweetener that has been used for decades but remains controversial due to existing debates over safety (Environmental Health Trust); and Sucralose, an artificial sweetener that is heat-stable and used in baking (“Sucralose”). These sweeteners offer a promising solution, and have been deemed safe by the Food and Drug Administration (FDA), World Health Organization (WHO), and European Food Safety Authority (EFSA). However, their safety has come under question.

Although these sugar substitutes provide a means to reduce calorie intake and address issues related to diabetes and heart health, questions continue to circulate about their extended safety. Every day dietary choices play a vital role in preserving long-term health, therefore leading to concerns about potential links between artificial sweeteners and cancer. Cancer, in biological terms, is a group of diseases formed by the uncontrolled division and growth of abnormal cells that invade surrounding tissue and can spread throughout the body via the blood system. These fast-growing cells disrupt normal bodily functions, often leading to serious health conditions if left untreated (Romanos-Nanclares, et al.). Cancer develops through a variety of genetic, environmental, and lifestyle factors including diet, exposure to carcinogens, and metabolic health. As millions of people worldwide are consuming them in place of traditional sugars, the universal consumption of artificial and natural sweeteners demands closer evaluation, specifically regarding the carcinogenic risks, in order to determine whether these substitutes truly bolster better health or simply exchange one health concern for another.

Sucralose

Sucralose is a chemically modified derivative of the disaccharide sucrose, in which three hydroxyl (-OH) groups have been replaced by chlorine atoms, yielding a chlorinated sugar analogue that is approximately 600 times sweeter compared to sucrose. It also possesses excellent thermal and hydrolytic stability–an attribute bolstering its widespread application in cooking, baking, and other high-temperature food processes (Magnuson et al. 681-682). The commercial production of sucralose includes selective chlorination of a protected sucrose followed by extensive purification of the intermediates and by-products to yield a stable sweetener for human consumption. In humans, sucralose is characterized by very restricted absorption: only about 15-27% of an ingested dose enters systemic (blood) circulation, while the vast majority (~70-85%) crosses the gastrointestinal tract intact and is excreted without change in the feces with the absorption fraction eliminated via the kidneys essentially unchanged (Chen et al. 1.1).

Because sucralose is not metabolized for energy and only minimally accumulates in tissues, this limited bioavailability has historically supported the assumption that it is biologically inert ("What Happens Consumes Sweetners"). As a result, Sucralose's practical applications extend broadly: it is featured in sugar-free desserts and snacks, chewing gum, diet sodas, pharmaceutical syrups, and as a tabletop packet sweetener. Notably, recent studies explore the toxicology of sucralose. Sucralose proved to exhibit genotoxic (specifically clastogenic) activity within in-vitro assays that assess DNA damage and chromosomal instability, and to impair human intestinal epithelial barrier integrity by reducing transepithelial electrical resistance and increasing permeability (Schiffman et al.). More precisely, in human gut-epithelium models, sucralose and its metabolite, Sucralose-6-acetate, induced significantly higher gene expression associated with oxidative stress, inflammation, and cancer-related pathways, such as Metallothionein-1G (MT1G) (Schiffman et al.). Sucralose-6-acetate is a structural analog impurity that appears and is also synthesized in small amounts during intestinal metabolism. Alternatively, a systematic mechanistic review applying key characteristics of carcinogens (KCC) found that sucralose shows an overall lack of "strong" activity across KCC's, and animal bioassays have not consistently demonstrated carcinogenic outcomes–findings that collectively underpin current regulatory assessments that sucralose is non-carcinogenic under typical exposure levels (Chappell et al.). While one study, along with a few others, identifies potential toxicology or carcinogenic issues, these may not be of physiological relevance, as changes do not occur until exposure at 10 mM. Doses that might be more physiologically relevant did not show any changes. In all, the weight of the evidence does not confirm a causal link between sucralose ingestion and human cancer.

Stevia

Stevia is an increasingly popular sugar substitute that is 400 times sweeter than sucrose, and commonly regarded as safe and "natural". It is extracted from the leaves of the shrub Stevia

Rebaudiana, indigenous to South America. The leaves contain a group of compounds called steviol glycosides, primarily stevioside and rebaudioside A, which give Stevia its sweeteners and are chemically extracted and purified for commercial use (Momtazi-Borojeni et al. 1). The absorption of these glycosides upon ingestion does not occur in the upper part of the digestive pathway; instead, they reach the colon largely intact, where gut microbiota break them down into their aglycone form, steviol, which is then absorbed and transported to the liver, where it is transformed via glucuronidation to steviol glucuronide before excretion in urine (Kasti et al.).

Given Stevia's extensive biochemical processing in the body, this metabolic sequence is surprising for a natural product. People generally cite stevia's botanical origin as evidence of its intrinsic safety. Indeed, high-purity steviol glycoside extracts (≥ 95 percent purity) have been granted "generally recognized as safe" status by regulatory authorities like the FDA, provided they are used within recommended limits ("GRAS Notice"). A comprehensive review of more than 900 mechanistic studies, many of which investigated benefits rather than carcinogenicity, found anti-inflammatory, antioxidant, and even antiproliferative effects (Chappell et al.). Supplemental pharmacological studies have elucidated several interesting therapeutic effects attributed to steviol glycosides, including anti-diabetic and anti-cancer activities; however, these effects are highly dose-dependent and are often observed in cell or animal models rather than in long-term human trials (Orellana-Paucar). The picture isn't as clear-cut as the "natural=safe" narrative might imply. Although current data do not strongly support a cancer risk, long-term human studies are sparse.

The core of the regulatory assessments comes from short-term toxicology and mechanistic data rather than decades of epidemiological research (Chappell et al.). Moreover, several in vitro studies indicate that Stevia may even exert cytotoxic effects on specific cancer cell lines, including breast and pancreatic cancer cell lines, but these promising preliminary results cannot substitute for robust long-term safety data in humans (Velesiotis et al.). Finally, while Stevia seems generally well-tolerated, some risks are present, with rare side effects such as bloating or dizziness; its impact on gut microbial composition, though potentially positive in several studies, is similarly not well understood (Kasti et al.). In other words, although stevia is "natural" in origin and has a relatively favorable short-term safety profile, its possible long-term risks, including any cancer implications, have not been adequately studied, and more research is needed before it is conclusively said to be safer than other sweeteners.

Aspartame:
Since the 1980's, Aspartame has been one of the most widely used food additives as an artificial sweetener in a variety of foods and beverages worldwide ("Aspartame Hazard"). Chemically, aspartame is the methyl ester of the dipeptide formed by L-aspartic acid and L-phenylalanine, and it yields a compound approximately 200 times sweeter than sucrose (Magnuson et al.). Aspartame is completely hydrolyzed in the gastrointestinal tract into three

components after ingestion–phenylalanine, aspartic acid, and methanol–each of which is metabolized by unique pathways (Griebsch et al.). Phenylalanine enters standard amino-acid metabolic cycles, aspartic acid participates in neurotransmitter and energy-related pathways, and methanol is converted into formaldehyde and then formate, which is eliminated at doses far beyond toxic thresholds (Butchko and Stargel). Individuals with phenylketonuria (PKU), a genetic disorder that prevents the normal metabolism of phenylalanine, must avoid aspartame entirely. This has further heightened scrutiny of the compound (Van Den Eeden et al.). Due to this metabolic breakdown, aspartame itself does not circulate systematically; however, this unique metabolic profile has also contributed to much of its scientific and public controversy.

Another aspect of its controversy, aspartame in part relates to earlier rodent studies that indicated possible carcinogenic activity. In the mid-2000s, large-scale lifetime rat studies conducted by the Ramazzini Institute reported leukemias, lymphomas, and mammary tumors following prenatal exposure at doses near or below the rodent equivalent of human acceptable intakes (Soffritti et al.). These findings spiked immense debate as more conventional two-year chronic toxicity studies in rats and mice had not documented comparable carcinogenic effects. Critics of the Ramazzini work particularly challenged the accuracy of tumor diagnoses, stating that many of the noticed pulmonary lesions might instead represent inflammatory reactions–perhaps due to microbial infections (ex. Mycoplasma pulmonis) – rather than true malignancies. Similarly, the European Food Safety Authority (EFSA) regarded “a substantial background incidence of chronic inflammatory diseases among rat populations” which may bias tumor incident estimates. Furthermore, the bioassays conducted by the Ramazzini Institute were not regarded by the EFSA and the U.S. FDA as “definitive bioassays for regulatory purposes.” In particular, “they were not conducted according to international standards…including Good Laboratory Practices (GLP) and formal peer review of pathology evaluation” as well as “deficits in study design, execution, and reporting of data provided” (“Comprehensive Review”). In response, the Ramazzini Institute recently re-examined all hematopoietic and lymphoid tissue (HLT) lesions from aspartame-exposed animals using immunohistochemical markers and morphological reassessment according to the latest International Harmonization of Nomenclature and Diagnostic Criteria for Lesions (INHAND) standard. The reanalysis confirmed malignancy in 92.3% of the originally diagnosed HLTs; only six lesions (roughly 8% of all HLTs) were re-classified (three as lymphoid hyperplasia, three as as chronic inflammation with fibrosis), and crucially, no evidence of Mycoplasma infection was found (Landrigan and Straif). Based on these results, the authors stand by their original conclusion that aspartame has properties a “chemical carcinogen” in rodents and reaffirm their previous findings that prenatal aspartame exposure at low doses and for a short latency increases cancer risk in the offspring compared to adults (Landrigan and Straif). Despite these studies suggesting this link, the majority of the scientific community shows concerns within the methods and experiments, leading to distrust in the results. Health agencies thus far have concluded that aspartame intake does not exceed established acceptable daily intakes (ADI) based on the available bioassays

and exposure assessments, while the more recent reevaluations incorporated updated exposure data during prenatal and early-life periods.

Human epidemiological evidence linking aspartame to cancer risk remains mixed and inconclusive. Several large cohort studies, including the NIH-AARP Diet and Health Study and the Nurses' Health Study, found no significant associations between aspartame intake and overall incidence of cancer (specifically breast cancer) (Romanos-Nanclares et al.). However, new analyses have raised concerns once again. A large prospective cohort study emanating from France–the NutriNet-Santé study, which followed more than 102,000 adults for eight years–reported the greater intakes of aspartame were associated with an increased risk of cancer, and the hazard ratio for breast cancer being around 1.22 (Debra et al.). Although these findings are especially compelling given the size of the study and specificity of diet, the authors underscored that such observational designs cannot prove causation and may reflect residual confounding. Nevertheless, the available, but limited, information about human exposure led the International Agency for Research on Cancer (IARC) in 2023 to classify aspartame as "possibly carcinogenic to humans" (Group 2B). Conversely, the FDA in the United States has indicated that aspartame is safe within its ADI level of 50 kg/mg body weight/day. Therefore, as seen through the evaluation of aspartame, the classification given to a substance may vary depending on the organization reviewing its safety, while still using the same substance in the same acceptable limits.

Comparisons Across Agencies

The stances of FDA, EFSA, and WHO on the regulation and science behind the safety of non-sugar sweeteners show broad agreement that, when appropriately used, certain sweeteners–puirifed Stevia (steviol glycosides), Sucralose, and Aspartame–are generally safe, though each organization has conditions of use, acceptable daily intake levels, or caveats for special populations, as summarized in Table 1.

The FDA has a mandate to regulate food additives under the U.S. Food, Drug, and Cosmetic Act. It explicitly approves aspartame and sucralose for use as food sweeteners, describing them as generally safe for the general population under the conditions reviewed ("Aspartame and Other Sweeteners"). For stevia, the FDA only considers high-purity steviol glycosides of at least 95% purity derived from the leaf as "Generally Recognized as Safe", and does not approve whole-leaf stevia or crude extracts; the leaf form remains unapproved for use as a sweetener ("Aspartame and Other Sweeteners"). The FDA has established acceptable daily intake levels for many of its approved high-intensity sweeteners, detailed below, underlining that safety evaluations include studies on metabolism, toxicity, and long-term effects ("Aspartame and Other Sweeteners").

EFSA similarly agrees with the safety of steviol glycosides, sucralose, and aspartame, within defined limits, as part of its role as the European Union's regulatory authority on food additives. In recent evaluations, EFSA has come to the conclusion that stevia-derived sweeteners, steviol glycosides, do not show signs of genotoxicity, carcinogenicity, or reproductive and developmental toxicity, hence setting an Acceptable Daily Intake (ADI) of 4 mg/kg body weight per day (steviol equivalents) (EFSA evaluates steviol glycosides). The 2023 EFSA evaluation of a newer fermentation-derived steviol glycosides, for example, rebaudioside M from yeast-based processes, reaffirmed this safety conclusion by noting no safety concern at proposed use levels ("Safety Evaluation Food Additive"). As for sucralose, EFSA considered reports of cancer risk–most notably one from 2016 with mice–and rejected them due to their defects in study design, lack of dose-response relationship, and absence of a plausible mode of action. EFSA reaffirmed that sucralose is safe and does not cause cancer, noting no evidence of in vivo genotoxicity (Chu). Similarly, aspartame is considered by EFSA to be safe when ingested within acceptable limits of 40 mg/kg bw/day (European Food Safety Authority).

WHO, which has a global representation, largely agrees with these conclusions on non-sugar sweeteners but frames them within its broader nutrition guidance. In 2023, WHO listed aspartame, sucralose, and stevia as some of the non-sugar sweeteners whose use should not be promoted for weight control since the evidence on long-term weight management and disease outcomes is weak and probably associated with unintended health risks. Although WHO does not ban these sweeteners, it advises that non-sugar sweeteners are "not essential dietary factors" and recommends a general reduction of exposure to sweetness ("WHO Advises").

Summary:
The consistent finding across FDA, EFSA, and WHO is that aspartame, sucralose, and purified stevia extracts–within limits–are considered safe to use. There are various differences, mainly in how each agency frames long-term public health guidance, especially regarding overall sweetness exposure and weight control policy rather than in verdicts about toxicity or carcinogenicity.

Stevia:
Purified steviol glycosides are approved by FDA and EFSA, with the ADI given as 4 mg/kg bw/day by EFSA. Crude leaf extracts remain unapproved under FDA in the U.S.

Sucralose:
It is approved by FDA for general use, and cancer risk issues have been evaluated and dismissed by EFSA–both consider it to be safe when used within established conditions of use. WHO has approved the usage of sucralose as well.

Aspartame:
All three agencies approve aspartame use, but some have suggested limits. It is approved for use by the FDA. According to EFSA, it is safe within its ADI. WHO lists it among the non-sugar sweeteners; at the same time, it advises caution regarding long-term daily use for weight control but does not ban it.

Conclusion and Further Recommendations:
Taken cumulatively, the present state of regulatory and scientific knowledge confirms that non-sugar sweeteners represent safe sugar alternatives from a technical standpoint but not conclusive positive agents of health improvement. FDA and EFSA approvals for food use have established that aspartame, sucralose, and purified steviol glycosides are likely not toxicologically dangerous if used within set limits; however, the very fact that such limits have to be set underlines the importance of their controlled use. Most importantly, safety levels do not necessarily imply positive nutritional value, while recently emerging scientific data casts further doubts on metabolic adaptation, behavioral patterns, and chronic exposure level (M and Vellapandian). Pragmatically, non-sugar sweeteners should not be used as the universal solution to weight management or excess sugar consumption issues. While agreeing with the general opinion on the short-term and medium-term safety expressed by the regulations, I concur with the WHO on its conservative approach to sweeteners being so integrated into our dietary culture in liquid drinks, snacks, and other pre-packaged items. From my conclusions here, reduction in sweetness preference rather than mere substitution is a strategy to be considered by consumers and policymakers alike. Staying within approved dietary guidelines while restricting usage on pre-packaged products with sweeteners and focusing on a dietary approach based on processed foods is, in my opinion, the best course based on available evidence.

Public Considerations and Real-Life Impacts:
Non-sugar sweeteners provide the greatest benefits when consumed sparingly and informatively. While individuals in the general public should not worry about regulating non-sugar sweeteners, they should be aware of all sources of exposure to these sweeteners over time and how their body responds to the sweetener. Individuals may combine many different food sources that contain non-sugar sweeteners into a single meal and may not know how much they are actually consuming. Thus, it is important to use sweeteners in moderation, especially for people who have metabolic disorders or intolerance to certain ingredients. Additionally, as children and adolescents develop, artificial sweeteners may have long-term impacts on their preferences for sweetness due to the sweetness intensity, which could ultimately impact their eating habits as an adult. For this reason, it is prudent to limit non-sugar sweetener intake in younger individuals as a preventive measure. Non-sugar sweeteners can

provide benefits, but for most individuals, they will be most beneficial when used sparingly with consideration, and they should not be considered an everyday sugar alternative.

Sweetener	Origin	Potential Cancer Risk	Metabolism	FDA Status	EFSA Status	WHO Guidelines
Stevia (purified steviol, ≥ 95%)	Natural	No evidence	Metabolized in the colon to steviol; then it is glucuronidated and excreted	Generally recognized as safe for purified forms; whole leaf unapproved	Approved; ADI: 4 mg/kg bw/day (steviol equivalents)	Approved; use is not promoted for weight control
Stevia (whole leaf / crude extract)	Natural	Not assessed	Metabolized same as above	Not approved	Not approved	Not promoted
Sucralose	Artificial	No evidence	Not metabolized; primarily excreted	Approved; ADI not established	Approved; no evidence of genotoxicity or carcinogenicity	Approved; similar guidelines on sugar intake
Aspartame	Artificial	No evidence at approved intake	Metabolized to Phenylalanine, Aspartic acid, and Methanol; Absorbed and processed	Approved; ADI: 50 mg/kg bw/day	Approved; ADI: 40 mg/kg bw/day	Approved; not promoted for long-term weight control; generally safe within limits

Table 1: This table recapitulates the evaluations concerning origin, metabolism, approval for use in the human diet and the assessment for carcinogenic risk associated with the most used non-sugar substitutes for sugar: stevia, sucralose, and aspartame. Generally speaking, all non-sugar sweeteners mentioned above have been assessed by the FDA, EFSA, and WHO, as safe for human consumption at current maximum levels of accepted daily intake (ADI expressed as mg/kg body weight [bw]/day) and have no credible evidence for carcinogenic risk.

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