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The Safety of Saccharin: An Analysis of Health Effects and Market Dynamics

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Abstract

Saccharin, chemically known as benzoic sulfimide ($C_7H_5NO_3S$), is an artificial sweetener with no calories and a high level of sweetness, approximately 300 to 400 times more than sucrose. Constantin Fahlberg first discovered and commercialized saccharin, and it quickly gained popularity due to its sweetness and affordability, leading to widespread use of the substance from pharmaceuticals to diet drinks in the early 20th century. Following its growth, saccharin faced significant controversy, primarily due to studies in the 1970s that linked it to bladder cancer in lab rats. These findings led to mandatory warning labels on products containing saccharin and regulatory bans in several countries. The controversy intensified with the 1958 Food Additive Amendment and the FDA's 1977 attempt to ban saccharin. By the early 2000s, health organizations such as the FDA reevaluated saccharin, declaring it safe for consumption, leading to the removal of bans and warning labels. Saccharin's global regulatory history highlights significant regional differences, and these regional variations underscore the complexities of saccharin's safety and regulation, emphasizing the importance of ongoing scientific review and adaptive policies. This paper seeks to determine the safety of saccharin and analyze the impacts of saccharin on human by considering the results of biochemical studies, epidemiological data, and experimental research. Findings suggest that saccharin is safe for consumption though contradictory data may suggest a need for continued research. This review acknowledges the challenges associated with conducting human-based versus animal-based studies but ultimately recommends further research on long-term effects and studies with human subjects when possible.

Keywords: Saccharin; Benzoic Sulfimide; Carcinogenic; $C_7H_5NO_3S$; Sweetener; Glucose Intolerance

1. Introduction

Saccharin, also known as benzoic sulfimide ($C_7H_5NO_3S$), is a synthetic compound utilized in many consumable products from beverages and candies to pharmaceuticals. It is made from toluene, the common name for methylbenzene, an inflammable aromatic hydrocarbon with a structure of benzene with one of its hydrogen molecules substituted with methyl. Its notable characteristics include its high-intensity sweetness with a slightly bitter and metallic aftertaste and its zero-calorie content.

The production of saccharin can either come from the Maumee method or Remsen & Fahlberg method. In the 1950s, O. Senn and G.F. Schlaudecker created a method of production using methyl anthranilate, available from phthalic anhydride, and the Maumee Chemical Company modified this procedure for use in commercial settings. This process is used by the only producer in the United States and consists of methyl anthranilate being diazotized, leading to the formation of 2-carbomethoxy benzenediazonium chloride (NCBI, 2024). Meanwhile, the Remsen & Fahlberg method

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goes through more than three cycles of water refinement, which makes the costs of production high, but at the same time it allows higher purity than the Maumee method without any impurities like organic solvents (Roth and Lück, 2016).

The Remson & Fahlberg method originated from Constantin Fahlberg, a chemist who worked on benzoic sulfimide in Ira Remsen's laboratory at Johns Hopkins University, who accidentally discovered saccharin in 1879 after sitting down for dinner after work and eating a bread roll without having washed his hands. The following year, in the published article with Remsen, he named the substance saccharin. In 1884, Fahlberg applied for patents and began the first commercial production of saccharin two years later in a suburb of Magdeburg, Germany. He later moved to New York and produced 5 kg of saccharin everyday with only one employee. During its early stages, saccharin's safety was doubted because it was made from toluene, which came from oil leftovers, specifically coal tar. However, the sweetener soon became famous for its sweetness and cheap price. Doctors started to prescribe saccharin for headaches, vomit, and obesity. Canners used saccharin as preservative, and patients of diabetes used it to sweeten their coffee. Saccharin was regarded as a cure for all, just like sugar was centuries ago (Hicks, 2010).

Over the years, saccharin has been the subject of extensive research and debate across the globe. One major question at the time regarded saccharin's safety due to skepticism about its artificiality. For many years, the only safety test done on saccharin was completed by Fahlberg in 1882 when he took 10g and waited 24 hours to notice any side effects (Hicks, 2010). Having seen no negative effects, he was assured of its safety. However, many European countries implemented restrictions on saccharin usage. In 1890, France had already ruled out saccharin as hazardous and banned production and import. Eight years later, the German government did the same with restrictions on usage and ban on food and drink. Spain, Portugal, Hungary, and more countries joined with similar actions. In 1902, Germany banned saccharin from all food and drinks except for patients who suffered from diabetes (Kim, 2016). In the United States, Harvey Washington Wiley was an early advocate for food regulation and raised concerns about saccharin's safety as early as 1906, but Theodore Roosevelt, who consumed saccharin himself, stifled regulatory actions. However, Upton Sinclair's publication of *The Jungle* in the United States acted as a catalyst for change in food safety, and Congress passed the first Pure Food and Drug Act soon after. The Food Additive Amendment of 1958, introducing the Delaney Clause, later marked a turning point by requiring the United States Food and Drug Administration to ban food additives shown to cause cancer in humans or animals (Hicks, 2010).

This affected saccharin production and consumption when early studies in the 1970s raised concerns about its potential link to bladder cancer in lab rats, leading to mandatory warning labels on products containing the sweetener. These warnings caused significant public concern and impacted saccharin's popularity. In 1977, the Food and Drug Administration (FDA) attempted to ban saccharin under the Delaney Clause following evidence linking it to bladder cancer in rats (Hicks, 2010). However, public outcry and industry lobbying delayed the ban, resulting in the requirement for warning labels on saccharin-containing products. The late 1970s witnessed a surge in saccharin sales amidst the controversy over its safety due to the free publicity (Hicks, 2010). As years passed, subsequent research failed to demonstrate a similar risk in humans, and further studies indicated that the bladder cancer findings were specific to the physiology of rats. The National Toxicology Program and the International Agency for Research on Cancer re-evaluated the information on saccharin available during the late 1990s (Touyz, 2011). The scientific basis for saccharin staying on the Environment Protection Agency's (EPA) hazardous substances list was no longer valid, and the agency removed saccharin from all of its lists. By the year 2000, warning labels were removed, and saccharin was declared safe for consumption by major health organizations, including the FDA and World Health Organization (WHO) (EPA, 2010).

As the history of saccharin reveals, its journey from a laboratory discovery to a widely used sweetener has been filled with controversy and scientific scrutiny. The argument that saccharin may cause bladder cancer became one of the biggest points of concern for people across the globe and played a significant factor in the implementation of these regulations. As time passed, researchers

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continued to conduct studies on saccharin, including its alleged carcinogenicity, allergic reactions, and effects on glucose and metabolic health. Despite initial safety concerns and regulatory challenges, extensive research and evolving scientific understanding have established saccharin's safety for human consumption. The purpose of this paper is to delve deeper into the scientific evidence surrounding saccharin and its alleged carcinogenicity and effect on glucose and metabolic health. We further analyze the effects of saccharin research on governmental regulation over the years and focus our attention on global patterns of saccharin consumption. Some of the issues that will be addressed include regulatory policies, cultural preferences, and economic consideration. By examining these aspects, we aim to provide a comprehensive overview of saccharin's role in modern dietary practices and its impact on public health.

2. Discussion

Carcinogenicity

The use of saccharin has been controversial since the 1970s because it was regarded as a substance that causes bladder cancer in rats. In these studies, researchers fed larger quantities of saccharin to the rodents, and these high dosages caused bladder tumors. Hence, saccharin was considered a potential carcinogen. However, subsequent studies researched these effects on both animals and humans, including an extensive review by the National Toxicology Program. Understanding dose-response relationships is crucial when evaluating the safety of chemicals, especially potential carcinogens. This means that the risk of harm from a chemical depends on the dosage taken, not just the presence of the chemical itself. For example, 50 million cups of instant decaffeinated coffee would equal the dose of trichloroethylene solvent needed for tumor formation in mice, and 82,000 pounds of bacon would reach the threshold levels of N-nitrosopyrrolidine found to cause cancer in rats. For saccharin, the equivalent of 800 twelve-ounce diet sodas with saccharin would be necessary to reach the carcinogenic doses that caused rat bladder cancer. Studies show that over a 5 month period, no harmful effects were observed on humans consuming 5 grams of saccharin daily (Touyz, 2011). Reaching this limit of 0.5 grams or 500 milligrams by one person is highly unlikely especially in a North American Diet. Despite initial controversy over the potential carcinogenicity of saccharin, further studies have found that extremely high doses of saccharin would be necessary to produce these negative effects, therefore indicating that saccharin does not present any significant risk of causing cancer in humans.

Effect on Glucose and Metabolic Health

Numerous studies have also investigated the effects of saccharin on glucose and overall metabolic health, finding contradictory results over the years. In August of 2014, SBS TV, a Korean broadcasting program, conducted a test to compare blood glucose change after consuming sugar and saccharin. A group of three people were given 30 grams of sugar, and then they measured changes in their blood glucose levels. The results for the three individuals were as follows: (1) 107 mg to 166 mg, (2) 98 mg to 132 mg, and (3) 129 mg to 221 mg. They were then given a saccharin solution, and when measured again, the results were as follows: (1) 132 mg to 96 mg, (2) 98 mg to 86 mg, and (3) 129 mg to 127 mg. A similar test by Dong Gil Kim yielded comparable results. The test subjects included 10 different volunteers; five of these volunteers drank 100 ml of 30% sugar solution. The blood glucose levels then rose as follows: 98 to 125, 105 to 119, 99 to 130, 117 to 147, and 90 to 106. On the other hand, the rest of the five volunteers took a saccharin solution and their blood glucose levels dropped as follows: 119 to 99, 120 to 118, 127 to 120, 96 to 91, and 134 to 128 respectively (Kim, 2016). These results suggest that saccharin leads blood glucose levels to decrease over time.

However, a separate study by Suez et al. (2014) conducted experiments on mice by feeding them saccharin and monitoring changes in gut microbiota and glucose tolerance and concluded that saccharin has adverse effects. In both conditions with lean mice and mice with a high fat diet, they found that the mice developed glucose intolerance. They also found that saccharin-consuming mice

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developed functional changes in their gut microbiota, therefore influencing their glucose tolerance (Suez, 2014). Furthermore, Azeez, et al. (2019) concluded that saccharin was unsafe for consumption in their study on saccharin consumption in rats. This study followed four groups of rats, including a control group and three groups given different doses of saccharin at 2.5, 5, and 10 mg/kg over the course of 120 days. They found that the latter two groups experienced an increase in body weight after 60 and 120 days and cited the results on glucose intolerance from Suez et al. as a potential reason for this phenomenon (Azeez, 2019). While both of these studies research the effects through animal-based trials, further studies with human participants have shown contradictory results.

A recent study by Serrano et al. (2021) conducted double-blind, placebo-controlled study on the effects of saccharin on gut microbiota and glucose tolerance and found that short-term consumption at the maximum acceptable levels did not result in any changes for healthy humans and mice. In this study, 54 participants were placed into one of four groups: placebo, saccharin, lactisole (STR inhibitor), or saccharin with lactisole, and they were given the maximum acceptable daily intake for 2 weeks. They also performed a 10-week study on mice and administered pure saccharin at a high dose in their drinking water. In both the humans and the mice, they did not find any effect on glucose or hormonal responses (Serrano, 2021).

Overall, the results of these studies seem to be inconclusive. Although initial studies on the effect of saccharin on blood glucose found saccharin to be beneficial to the human body, other studies questioned whether saccharin reduced glucose tolerance. The most recent results by Serrano et al. (2021) seem to demonstrate that saccharin does not have any adverse effects on glucose when taken at the acceptable daily limit. It is notable that the studies with human subjects did not find saccharin to negatively influence glucose tolerance and metabolism. Further studies may need to research whether there is a biological difference in humans and rodents that would generate this type of discrepancy in the results.

Regional Regulatory and Market Dynamics: A Global Perspective

The global shape of saccharin consumption varied regulatory approaches, cultural preferences, and economic conditions in different regions. Europe, for example, took a cautious approach to saccharin from the beginning. In the late 19th and early 20th centuries, European countries like France, Germany, Hungary, and Portugal imposed bans or severe restrictions on saccharin, influenced by reports of adverse health effects. These early decisions were not solely based on scientific evidence but were also shaped by socio-political elements, including economic pressures from the sugar industry, which viewed saccharin as a competitive threat (World Agricultural Strategies, 2019). As a result, saccharin use in Europe has remained limited, with consumers and regulators favoring alternatives perceived as safer.

Canada's experience with saccharin reflects aspects of both the European and American approaches but with its own unique regulatory twists. Initially, Canada was cautious, following Europe's lead and outlawing saccharin in 1914 over worries about possible health hazards. This ban remained in place for decades, reflecting a strict approach to food safety that prioritized consumer protection. However, by the mid-20th century, as demand for low-calorie sugar alternatives grew and new scientific evidence emerged, Canada reevaluated its stance. In 1977, Health Canada lifted the saccharin ban, but with strict labeling requirements to ensure consumers were informed about its presence in food products (Health Canada, 1977). This balanced approach allowed saccharin to re-enter the Canadian market while maintaining a level of caution, demonstrating Canada’s commitment to both consumer safety and choice. Today, saccharin is available in Canada, but its market share remains modest compared to other sweeteners, influenced by the country’s historically cautious regulatory stance.

South Korea’s approach to saccharin presents a contrasting regional perspective, shaped by socio-economic factors and the rapid industrialization that followed the Korean War. In the early post-war period, saccharin was embraced with minimal regulatory oversight, driven by the urgent need for affordable food additives. The lack of initial regulation allowed saccharin to become widely

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used across various food products, from beverages to everyday meals. This necessity during a crucial period of recovery laid the foundation for saccharin's sustained popularity in Korea. Over the decades, saccharin's integration into the Korean diet has been reinforced by the country's cultural preferences, which heavily favor sweet flavors. This is evident in the frequent use of saccharin in various processed foods, such as sodas and snacks, and even in traditional home-cooked dishes. The economic advantage of saccharin, being less expensive than sugar and other sweeteners, has solidified its position in Korean cuisine, making it a daily part of consumption. As South Korea's economy grew and its public health infrastructure developed, the regulatory environment gradually evolved. By the late 20th century, South Korean authorities began to tighten regulations on saccharin, influenced by international studies suggesting potential health risks (Bahndorf, 2004). These changes included setting permissible limits for saccharin in food products and requiring mandatory labeling to inform consumers. Despite these stricter regulations, saccharin continues to be widely used in Korea, largely due to its cost-effectiveness and deep-rooted presence in the food culture.

The United States, with its regulatory rollercoaster, offers yet another perspective on saccharin's global market dynamics. Initially, saccharin was introduced to American consumers during World War I and II when sugar was rationed, and alternatives were needed. Its adoption during these periods was driven by necessity, similar to Korea's experience, but the American market's response to saccharin evolved differently over time. Following the wars, the creation of new artificial and natural sweeteners, such as high fructose corn syrup, stevia, and honey, offered American consumers a broader range of options (Health Canada, 1977). These ranges caused the market for saccharin to slowly fall in cost. The temporary ban in the 1970s, followed by the FDA's eventual reversal of the decision, created significant market instability and affected consumer trust. The U.S. market's complexity is further heightened by the availability of a diverse range of sweeteners, which have fragmented consumer preferences. While saccharin remains in use, it competes with a variety of other sweeteners, each catering to different segments of the market. The introduction of high fructose corn syrup and natural sweeteners like stevia has further diluted saccharin's presence, leading to a more competitive and varied market landscape.

This comparative analysis underscores how regional regulatory environments, cultural attitudes, and economic factors have collectively shaped saccharin consumption patterns across the globe. In Europe and Canada, early bans and cautious regulatory approaches led to reduced saccharin use and a more negative perception of its safety. South Korea, on the other hand, maintained a more relaxed stance initially, allowing for widespread saccharin use, with regulations tightening only after international studies raised health concerns. Meanwhile, the U.S. has experienced a fluctuating regulatory environment, which, combined with the availability of alternative sweeteners, has resulted in a more complex and competitive market dynamic for saccharin.

These regional differences highlight the importance of understanding the broader context in which saccharin is consumed. Policymakers and industry stakeholders can learn from these diverse experiences to design strategies that address consumer preferences, market demands, and regulatory challenges in different regions. The global landscape of saccharin use is a testament to how historical, cultural, and economic factors converge to shape the consumption patterns of even the most

3. Conclusions

Despite controversy in the 20th century, further research has indicated that saccharin is safe for human consumption, and saccharin has continued to prevail in the global market. Although initial research suggested that saccharin was carcinogenic, research on dose-response relationships has since demonstrated that saccharin is not carcinogenic when taken at the acceptable daily limit. However, additional research on saccharin's effect on glucose tolerance has highlighted the importance of continued research in this field. Results of these studies remained contradictory, but recent research on human consumption of saccharin indicated that saccharin is safe for use. Nevertheless, these studies have emphasized the need for further research in the field.

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Further research may include studies on long-term effects. Although studies have attempted to research the long-term effects of saccharin, this area of the field currently remains insufficient. Most of the research concerns short-term effects, which will not provide a comprehensive view of saccharin's impact on human health. Long-term studies may provide necessary information on the effects of saccharin over time as well as the difference in effects on people with varying health conditions. This could provide information for groups of people with genetic predispositions or varying health conditions and help advise whether or not saccharin consumption would be beneficial for their specific circumstances.

Another focal point for future research includes investigating the effects of saccharin specific to the human body. Much of the current literature surrounds experimentation on laboratory animals, which cannot imitate the true metabolic state of the human body. Although studies involving human subjects may have limitations, the full effects of saccharin may remain unknown without information specific to the conditions of the human body. The 1970s controversy over saccharin's alleged carcinogenicity uncovers the importance of rigorous research and experimentation, which we can use as a precedent for the future.

As a result of saccharin's global controversy, saccharin's market dynamics have changed significantly over the years. Research on saccharin's carcinogenicity strongly influenced the implementation of bans in several different countries. Once further research emerged, contradicting initial studies, consumers responded in different ways. Saccharin remains a widely used sweetener, mainly because of the growing consumer demand for low-calorie foods. Even so, ongoing debates and conflicting studies over safety have made the market cautious. Therefore, regulatory bodies and health professionals have recognized that accrued benefits must be weighed against probable risks, putting into perspective the importance of informed consumer choices. Ultimately, further research must be conducted not only to inform consumers on an individual level, but to inform governmental officials when considering how to approach regulations on the food industry and the prioritization of public health.

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