THE METABOLISM AND TOXICOLOGY OF SACCHARIN


Department of Biochemistry, Ahmadu Bello University, Zaria-Nigeria.

Department of Biochemistry, Kogi State University, Anyigba, Kogi State Nigeria

Department of Animal Science, Ahmadu Bello University, Zaria-Nigeria.

ABSTRACT
Saccharin, one of the sweeteners in the world, is still regarded as a carcinogen and diabetic inducer in some parts of the world. Concern peaked in 1977, after publication of a study indicating an increased rate of bladder cancer in rats fed large doses of saccharin. In 1977, Canada banned saccharin while US-FDA also proposed a ban. In due course, US congress required all saccharin-containing foods to display a warning label indicating that saccharin may be carcinogenic. This resulted in the carcinogenicity, genotoxicity, hepatotoxicity and teratological studies of saccharin in animals including humans by the most highly reputable global health and credible science organizations worldwide. None of these studies ever showed a clear causal relationship between saccharin consumption and health risks in humans at normal dosage. Ultimately, the influential 1977 study was later criticized for the high dosages of saccharin that were given to test subject rats. Consequently, the US-FDA formally withdraws its 1977 proposal to ban the use of saccharin and the National Toxicity Program announced the delisting of saccharin as a carcinogen. Therefore, use of saccharin can bring about a healthy lifestyle free of calorie accumulation and the risk of obesity with its associated cardiovascular complications.

Key Words: Saccharin, Carcinogen, Sweetener, Toxicity

INTRODUCTION
Saccharin, a petroleum derivative is a white crystalline artificial sweetener that is about 200 to 700 times sweeter than sucrose. It is one of the most studied food ingredients and the foundation of many low-calorie and sugar-free products around the world. It is one of the oldest of non-nutritive sweeteners, whose use is allowed in the US, but banned in other countries [1, 2, 3, 4].

Origin of Saccharin: Saccharin was serendipitously discovered in 1879 by Constantine Fahlberg, a chemist of Johns Hopkins University as one of the first artificial sweeteners on earth.

This happened when he was researching the oxidative mechanisms of toluenesulfonamide while working on coal tar derivatives in the laboratory of Ira Remsen. Accidentally, he spilled a chemical on his hand. Later on, while eating dinner, Fahlberg noticed a more sweetness in the bread he was eating, he licked his finger and noticed that the substance had a sweet taste [5, 6, 2, 7]. Through careful examination, he traced the sweetness back to the chemical, later named saccharin, by tasting various residues on his hands and clothes and finally chemicals in the laboratory. In 1879 and 1880, Fahlberg and Remsen published articles on benzoic sulfinide. Fahlberg described the methods of producing this substance that he named saccharin when he was in New York City working on his own in 1884 [5]. Since the time of saccharin discovery, a number of compounds have been discovered and used as food additives for their sweetening properties. Its use has been since 1900, but obtained FDA approval in 1970 [7]. By 1907, saccharin was used as a replacement for sugar in foods for diabetics.
Since it is not metabolized in the body for energy, saccharin is classified as a non-caloric sweetener. By the 1960s it was used on a massive scale in the "diet" soft drink industry [2]. Consequent upon sugar shortage during the World War I, saccharin became widespread and commercialized. Since saccharin is a calorie-free sweetener, its popularity further increased during the 1960s and 1970s among dieters [2]. In the United States, saccharin is often found in restaurants in pink packets; the most popular brand is "Sweet 'N Low". Saccharin is used to sweeten products such as drinks, candies, medicines, and toothpaste, canned fruit, jams, salad dressing, chewing gum, table top sweeteners, baked goods, jams, and dessert toppings etc [2]

CHEMISTRY OF SACCHARIN
Structure of Saccharin: The chemical formula of saccharin is C₇H₅NO₃S and the basic substance in it is benzoic sulfimide. It has a pKa value of about 2.0. It can be used to prepare exclusively disubstituted amines from alkyl halides using Gabriel synthesis. The chemical structure of saccharin is diagrammatically represented Figure 1.

Nature of Saccharin: Saccharin is a white crystalline solid with a molecular mass of 183.18g mol⁻¹ and a density of 0.828g/cm³. It has a melting point of 228.8 – 229.7°C. Even though saccharin has about 200 – 700 times the sweetening power of sucrose, yet it has an unpleasant bitter or metallic aftertaste, especially at high concentrations.

Taste of Saccharin: It is still unclear as to the reason for the sweet taste of saccharin. However, scientist has proposed that it might be due to its shape which fit into the specific receptor site in the taste buds. Evidence for this comes from the fact that if the shape is modified slightly, say by changing the H on the nitrogen to a methyl, the new molecule no longer tastes sweet. Perhaps the specific taste receptors it targets are peculiar to humans, in view of the fact that bees or butterflies, which normally crave the sweetness of nectar, do not treat it as a pleasing substance. [2].

Effect of Heat on Saccharin: Saccharin is stable to heat unlike the newer artificial sweetener aspartame, but it does not react chemically with other food ingredients. Blends of saccharin with other sweeteners are often used to compensate for each sweetener's weaknesses [5, 8].

Solubility in Water: The solubility of Saccharin in water is about 1g per 290 ml. In its acidic form it is insoluble in water. The sodium salt form is usually used as an artificial sweetener. The calcium salt is also used at times, particularly by people restricting their dietary sodium intake. Both salts are highly water-soluble; usually about 0.67 grams per milliliter water at room temperature. [5, 8].

Synthesis of Saccharin: Saccharin can be synthesized through the initial reaction between toluene and chlorosulfonic acid. It is then converted to a sulfonamide with ammonia, and oxidized to a benzoic acid then heated to form the cyclic imide [5, 9]. The yield from this method is very low. An improve method was developed in 1950 at the Maumee Chemical Company of Toledo. In this production method, anthranilic acid successively reacts with nitrous acid, sulfur dioxide, chlorine, and then ammonia to produce saccharin. Another route begins with o-chlorotoluene. It is also known as ortho sulfobenzoic acid [10]. A series of different chemical impurities could find their way to the final product, hence the most widely used methods for the production of saccharin are the Remsen-Fahlberg and the Maumee processes.
METABOLISM OF SACCHARIN

Ingestion: Upon ingestion, saccharin goes through the human digestive system without being digested, for this reason it is not absorbed or metabolized. It is excreted, unchanged, via the kidneys. On this bases that saccharin is not metabolized, the FDA of the United States considers this compound safe [7]. Although saccharin has no food energy value, yet it can trigger the release of insulin in humans and rats due to its taste [11, 12, 13].

Absorption: The absorption of saccharin depends on various factors, such as the pH value and the pKa of the animal. In most animals including man, absorption of saccharin occur rapidly with a pKa of about 2.0-2.2. Saccharin exists in acidic media predominantly in the unionized form, which is the more readily absorbed form in a number of animal species. In the stomach of rabbit and guinea-pig, saccharin is absorbed completely at a pH of 1.9 and 1.4 respectively, when compared with the stomach of rat at a pH 4.2 [14, 15]. In monkeys, and also most probably in man, both gastric acidity and degree of absorption are intermediate between those of the rabbit and guinea-pig on one side, and the rat on the other [14]. Which means the degree of absorption of saccharin could be dependent on food intake which affects the acidity of the gastric contents.

Distribution and Excretion: Notable researcher, including Lethco and wallace [16] studied the distribution of radioactivity in organs and tissues of rats at various time intervals (1, 2, 4, 8, 24, 48 and 72 hours) following a single oral administration of (3-14C) saccharin (50 mg/kg). Approximately one hour after dosing, Traces of radioactivity were found in almost all organs. It was found that brain and spleen contained only minute quantities of 14C., while Kidney, urinary bladder and liver contained the highest amount of 14C, which peaked at 4 and 8 hours. In subsequent experiments, rinsing the bladders of the treated rats with 8, 0.5 ml portions of a 0.9% saline solution, they found that a significant portion of the 14C activity was retained by or bound to the bladder tissue [16].

TOXICITY STUDY OF SACCHARIN

Carcinogenicity Study: Following the investigation research report of Harvey W. Wiley that saccharin poses digestive problem [17], worries arose among man regarding the safety of saccharin. In responds to the issue by the then president of the United States of American Theodore Roosevelt (who was at the time dieting too on orders from his medical doctor to lower his risk for diabetes) said to Wiley Harvey that “Anyone who thinks saccharin is dangerous is an idiot” [17].

The concern that saccharin might be an animal carcinogen all through the “60s as suggested by various studies that was conducted in experimental models peaked up in 1977 [17] consequent upon the publication that saccharin increases the rate of bladder cancer in rats fed with large doses of saccharin. This led to the ban of saccharin in China and its proposed ban in the United State by the US FDA. At the time, saccharin was only artificial sweetener available in the U.S and the proposed ban met with strong public opposition, mostly by the diabetic persons. In the long run, the U.S congress placed a moratorium on the ban, requiring instead that all saccharin-containing foods display a warning label indicating that saccharin may be a carcinogen. Series of experiments have been conducted on saccharin with some showing a correlation between consumption and increased bladder cancer and others showing no such correlation. An obvious relationship between saccharin and health risks in human subjects at normal doses have never been established in any study till date, but the correlation between consumption and cancer have been shown in some studies [17].

The biological mechanism believed to be responsible for the rats’ cancers has been shown to be inappropriate to humans, as a result of the difference in urine composition between rats and human. Many of the rat cancer may have been caused by contamination from the rubber plungers inside syringes, the rubber seals used may corrode when mixed with certain fluids and decomposed rubber may have caused the bad results. Others blame certain types of rats like the Fischer 344 Rat which became a poor example specimen for testing cancers when it was found out that these laboratory animals developed cancer spontaneously, when injected with pure water only [9]. The FDA of the U.S. in 1991, formally withdraw its proposed 1977 ban on the use of saccharin. But in 2000, the U.S congress repealed the law requiring saccharin products to carry health warning labels.

Toxicological Study: Studies on saccharin exposure reveal that it has both positive and negative effect, such as the possibility to induce cancer in rats and dogs, hence the first attempt at banning saccharin came in 1911, when a group of federal scientists categorized it as an “adulterant” not suitable for general use in foods, though the same group later approved its use in products “for invalids” [18]. The review conducted in 1983 by Arnold provide information on two-generation saccharin bio-assays. In the researching of the potential effects of substances, at least two generation studies are beneficial. With respect to the studies, animals were exposed to saccharin, at all stages of development (i.e., in uteri, during lactation, and in feed as an adult). Only three
studies of saccharin used a two-generation model, as at the time of Arnold’s publication. These studies categorically demonstrated that when rats were exposed to diets containing 5% or 7.5% saccharin from the time of conception to death, an increased frequency of urinary bladder cancers was found, mostly in males. There was an observation of the fact that saccharin is not metabolized, it is nucleophilic and does not bind to DNA. But, it does suppress humoral antibody production in rats. At dosages of 5% or greater, saccharin does not act as a typical chemical carcinogen, based on the theory that all carcinogens are strong electrophilic agents [4]. The finding from the study above lead to the prohibition of saccharin in Canada and a proposed ban in the United States [6, 19].

In 1991, the U.S. withdrew her proposed ban, but foods containing saccharin were required to carry a warning label [20, 19]. To indicate that “saccharin is a potential cancer causing agent,” a warning label was placed on all products containing saccharin. Current research showing the safety of this product led to this decision being overturned in 2000 [21]. Though, a ban on saccharin still exists in Canada, having considering the fact that series of toxicological evidence and the lack of a consistent association in epidemiological studies the Health Canada suggests that carcinogenic effects of saccharin noted in rats are not relevant to humans. Hence, they are considering re-listing saccharin as a food additive in the Canadian Food and Drug Regulations for use as a sweetener in the proposed food categories [22, 19].

**Hepatotoxicity Study:** In 1992, Kumar, et al. reported that saccharin posed no threat to liver function [23]. It was also reported that in a patients who had elevated serum concentrations of liver enzymes after the oral administration of three different drugs, of which saccharin was the only common constituents, re-exposure to pure saccharin supported its role in the pathogenesis of liver damage in the patients. The pathogenesis of saccharin hepatotoxicity in these patients is unclear. Symptoms suggestive of hypersensitivity were absent. Saccharin is not metabolized in vivo, being in an almost unmodified form in the urine, and it does not accumulate in the liver. The small amount of saccharin (never exceeding 16 mg daily) taken by patients underscores the idiosyncratic nature of the reaction [23, 24].

**Teratology Study:** Till date, the teratogenic study of saccharin with mice has always been negative. In an experiment conducted on feeding pregnant female rats with diets containing 0.3% saccharin throughout the gestation period shown that the pups from saccharin treated dams had a 37.9% incidence of lens anomalies versus 12.4% incidence for the control animals [25].

**Genotoxicity Study:** Several in-vitro and in vivo studies have shown clastogenicity, specifically at high concentrations in in-vitro studies [26, 27]. In several in-vitro studies for induction of chromosomal aberrations in Chinese hamster cells and in human lymphocytes, sodium saccharin was found weakly positive [27, 28]. By and large weak responses were observed in some in-vitro assays at the chromosomal level. However, these were only seen in high concentrations and it is possible that they are attributable to ionic imbalances which are known to cause non-specific effects. There are also conflicting reports from in vitro studies, but some cases the materials use was found or known to contain impurities or contaminants from the manufacture of saccharin [29].

**Epidemiological Study:** Series of evidence comes from the now numerous epidemiological studies on saccharin which have included studies of groups consuming relatively high levels of saccharin. In a review by Chappel, [30]; Elock and Morgan, [31], it was indicated that there is no detectable association between artificial sweetener consumption most in particular saccharin and bladder cancer in humans. Various epidemiological studies indicates no increase in the occurrence of bladder tumours in human from the ingestion of saccharin, including in individuals with the highest consumption rate of artificial sweetened beverages and those using saccharin as a table-top sweetener.

**Beneficial Usage of Saccharin:** All over the world, Food and beverages industries have over the century found the use of saccharin imperative due to its absence of carbohydrate and no calorie value. For example, in Europe, the use of saccharin became more considerable after the two world wars. Several generations of Americans has made the use saccharin an integral part of their daily lifestyle in the United State. Most in particular, the diabetic individuals whose diets require a restriction of caloric or carbohydrate intake. A good number of health practitioners support the use of a non-caloric sweetener like saccharin in weight reduction and for people with diabetes [21].

According to the Calorie Control Council Research (CCC), Health professionals believe saccharin is especially beneficial to persons with diabetes and the obese, and helps reduce dental cavities. According to opinion research, people use saccharin to stay in better overall health, control weight or maintain an attractive physical appearance. In another report of the CCC, No low-calorie sweetener is perfect for all uses. But, a range of sweeteners enables the development of a much wider range of new, good-tasting, low-calorie
products to meet consumer demand. Also, an array of low-calorie sweeteners provides products with increased stability, improved taste, lower production costs and more choices for the consumer [21].

Saccharin is important for a wide range of low-calorie and sugar-free food and beverage applications. It is used in such products like soft drinks, tabletop sweeteners, baked goods, jams, chewing gum, canned fruit, candy, dessert toppings and salad dressings. It is also used in cosmetic products, vitamins and pharmaceuticals. One of the most popular uses of saccharin is in the production of the product called “Sweet ‘N Low®”, a tabletop sweetener in the United States [21,30].

GLOBAL REPORTS ON THE SAFETY OF SACCHARIN

Over the years, series of researchers, corporate bodies and individuals have worked on saccharin. The most highly reputable global health and credible science organizations have these comments to say with respect to the evaluation and confirmation on the safety of saccharin as it relate to human subjects.

The National Cancer Institute in its "Cancer Facts" documents reviewed in 2009 stated that ‘epidemiological studies do not provide clear evidence’ of saccharin’s link to human cancer.

The World Cancer Research Fund Stated in the American Institute for Cancer Research 2007 reported on page 143 that the evidence from epidemiological studies does not suggest that artificial sweeteners have a detectable effect on the risk of any cancer [32].

The American Dietetic Association “Use of Nutritive and Non-nutritive Sweeteners” position statement, on July 1993. States that "Evidence gathered from the numerous animal and human studies of saccharin does not suggest that there is any significant risk to the human population from the normal use of saccharin.

Members of the British Medical Association Advised in the British Medical Journal, that "The major benefits of saccharin are; an improved quality of life, low cost, and stability at warm temperatures. A small risk for bladder cancer continues to be found in male rats exposed to high doses of saccharin. However, epidemiologic studies show no evidence of a carcinogenic effect in man [33].

The Health Protection Branch of the Health and Welfare Canada, on December 5, 1991 declared that "Epidemiological studies have also not established any evidence that bladder cancer in man is associated with saccharin intake [33, 34].

CONCLUSION

The Joint Expert Committee on Food Additives (JECFA) of the World Health Organization and the Scientific Committee for Food of the European Union has reviewed and certified the safety of saccharin. As of today, saccharin is approved in more than 100 countries around the world. It can therefore be recommended as one of the very best choice for diabetic patients and those dieting. Therefore, use of saccharin can bring about a healthy lifestyle free of calorie accumulation and the risk of obesity with its associated cardiovascular complications.

REFERENCES

2. Ophardt CE. Saccharin - the oldest Sweetener Sweet ‘N Low, Sugar Twin. V.Chmbook 2003, 549


