SACCHARIN GENOTOXICITY AND CARCINOGENICITY: A REVIEW

Aslı Uçar[1] and Serkan Yilmaz*[2]

[1] Ankara University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Aktaş Kavşağı Altındağ, 06340, Ankara, Turkey
[2] Ankara University, Faculty of Health Sciences, Department of Midwifery, Aktaş Kavşağı Altındağ, 06340, Ankara, Turkey

ABSTRACT

In this study, it was aimed to review saccharine's genotoxicity and carcinogenicity. Saccharine is one of the most common sweeteners like aspartame, acesulfame K, and cyclamates. It is not metabolized in the gastrointestinal (GI) tract and, therefore, does not affect blood insulin levels. Saccharine -300 times sweeter than sucrose- is commonly used in many foods like soft drinks, baked goods, jams, canned fruits, candy, salad dressings, dessert etc. Because saccharine is consumed by millions of people, including children and even fetuses, it takes great public health significance, and great of interest to the public about its safety. Too many studies have been done for the safety of saccharine. In this study, it was reviewed the all literatures between 1975 and 2014 about saccharine's safety. According to the literature, genotoxicity and carcinogenicity of saccharine is still confusing. So, consumers should be careful to the consumption of this artificial sweetener.

KEYWORDS:
Saccharine, safety, genotoxicity, carcinogenicity, nutrition

1. INTRODUCTION

Artificial sweeteners are used as sugar substitutes in called "zero" or "light"- beverages, foodstuffs, pharmaceuticals and personnel care products [2]. They have been used by consumers to achieve a sweet taste, for reasons of economics, blood glucose control, or energy control [2]. The most common sweeteners are aspartame, acesulfame K, saccharin, and cyclamates. The first generation of the sweetener saccharin was produced in 1878 by Constantin Fahlberg [3]. Although saccharin was commercialized not long after its discovery, it was not until sugar shortages during World War I, that its use became widespread. Its popularity further increased during the 1960s and 1970s, since saccharin is a calorie-free sweetener [3]. Saccharin was originally listed as GRAS. FDA proposed a ban on saccharin under the Delaney Clause because of an association with bladder cancer in laboratory animals in 1958 [2]. Not convinced of saccharin's safety, because of the (inconsistent) evidence of bladder tumors in saccharin-treated F1 male rats, the FDA proposed a ban on its use as a food additive [4]. In 1996, the ban was withdrawn and the zero-risk standard changed to one of "reasonable certainty of no harm." In 2000, saccharin was widely used, often in combination with other sweeteners [2].

Saccharin (1,1-dioxo-1,2-benzothiazol-3-one) is 300 times sweeter than sucrose [5]. It is not metabolized in the body and is heat-stable [6]. In the food industry, it is commonly used in soft drinks, baked goods, jams, canned fruit, candy, salad dressings, dessert toppings, and chewing gum, in addition to being used as a tabletop sweetener. An important characteristic of saccharin is that its sweetening power is not reduced when heated, which makes it an excellent candidate as an additive in low-caloric and sugar-free products. Saccharin is not metabolized in the gastrointestinal (GI) tract and, therefore, does not affect blood insulin levels [7]. For the risk characterization of non-nutritive sweeteners, the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) had established an acceptable daily intake (ADI) of 5 mg/kg body weight for saccharin (SAC), European Union, US FDA, Japan, France, China and Taiwan [8]. As per a 2010 report in Current Oncology, one would have to drink about 800 twelve-ounce diet sodas containing saccharin to reach doses that can induce carcinogenesis [9].

Concerns with regard to the safety of saccharin are of great public health significance and of great interest to the public, because saccharin is consumed by tens of millions of people, including children and even fetuses. Any evidence of carcinogenesis -- and there is ample such evidence -- of such a widely used chemical should spur health officials to minimize human exposure to it [10]

There are lots of studies about saccharin effects on health. Some studies found that use of saccharin is associated with an increased feeling of hunger [11-13]. A rat study showed that their diets were sweetened with saccharin for over 5 weeks, presented greater weight gain and adiposity, as well as a decrease in the central body temperature, when compared to glucose supplementation [14]. In another study, it was found that when taken together, the use of aspartame, acesulfame, cyclamate and saccharin in

foods may be considered as safe, with regard to no effects on CYP1A1 induction and activation of AhR and GR receptors [15]. A few epidemiological studies also found some relationships between saccharin and bladder cancer risk in humans [16-19], but most – and the largest – studies found no association [20-22]. In this study, we aimed to review geno-toxic and carcinogenic effects of saccharine.

2. METHODS

This survey was conducted to gather available information and providing an overall perspective on the genotoxicity and carcinogenicity of saccharin. A literature search on genotoxicity and carcinogenicity of saccharin was performed in the Pubmed, Scopus, Web of Science, Science-Direct databases from year 1975 to 2014 (October). From the published literature, 11 genotoxicity studies and 13 carcinogenicity studies were analyzed.

3. RESULTS

3.1 Genotoxicity

In reports of IARC [23, 24], Ashby [25], Tennant [26] and Williams [27], saccharin was not active in *in vitro* short-term and *in vivo* genotoxicity tests. However, it has been found to induce SCE in human lymphocytes and plant cells *in vitro,* at doses as high as 25–50 mM [28]. Jeffrey and Williams [29] tested the geno-toxic activity of saccharin in the rat hepatocyte DNA repair assay (from F344 and Sprague-Dawley rats). Authors have reported that saccharin was negative in this assay. Sasaki *et al.* [30] determined the genotoxicity of sodium saccharin in male ddY mice using comet assay on the glandular stomach, colon, liver, kidney, urinary bladder, lung, brain, and bone marrow, and 24 h after treatment. A hundred, 1000 and 2000 mg/kg doses for 3-h treatment and 2000 mg/kg dose for 24-h treatment were orally administered to male mice. Sodium saccharin significantly increased the DNA damage in the glandular stomach and colon. Bandyopadhyay *et al.* [31] evaluated the mutagenicity of the saccharin in the Ames/*Salmonella*/microsome test and their genotoxic potential by comet assay in the bone marrow cells of Swiss albino mice. Fifty, 100, and 200 mg/kg bw of saccharin was orally administered. The comet parameters of DNA were increased in the bone marrow cells due to the sweetener-induced DNA strand breaks. However, none could act as a potential mutagen in the Ames/*Salmonella*/microsome test. Icsel and Yılmaz [32] reported the interactions of fish sperm DNA (FS-DNA) with the sodium salt of sweetener saccharin, and its copper and zinc complexes. They used UV–VIS titration, fluorometric competition, thermal denaturation, viscosity and gel electrophoresis measurements. They have reported that Na(sac) and its metal complexes showed a moderate DNA binding affinity. Frenzilli *et al.* [33] investigated the *in-vitro* activity of saccharin using alkaline and neutral comet assays in human leukocytes. Zero, 1, 5, 25 and 50 mM concentrations of saccharin were used for each experiment. In the first experiment, no effects were observed in alkaline conditions, whereas a significant increase at the dose of 50 mM at pH 8 was detected. In the second experiment, negative results were obtained under both pH conditions. Authors have concluded that saccharin is negative in the SGCE assay.

3.2 Carcinogenicity

There has been some controversy about the carcinogenicity of saccharin in the past. Some feeding studies indicated that saccharin at high dosage produced tumors; however, several animal studies demonstrated no carcinogenic effect of saccharin. Munro *et al.* [34] investigated the carcinogenicity of saccharin in groups of 60 male and 60 female Charles River rats; 0, 90, 270, 810, or 2430 mg saccharin/kg/day were administered to the animals for a period of 26 months. Food consumption, body weight, and clinical examinations were conducted weekly on all rats. Four bladder tumors were found in the treated animals. The tumors were transitional cell papillomata. However, saccharin administration was not accompanied by an increase in tumor incidence, although high doses were associated with reduced body weight in both sexes, and decreased

TABLE 1 - Sum of the genotoxicity of saccharin.

Test material	Genotoxic end-point	Results	References
in vitro short-term and *in vivo* genotoxicity tests		-	IARC [23, 24], Ashby [25], Tennant [26]and Williams [27]
Human lymphocytes	Sister chromatid exchanges	+	Zhang et al. [28]
Plant	Sister chromatid exchanges	+	Zhang et al. [28]
F344 and Sprague-Dawley rats	Rat hepatocyte DNA repair assay	-	Jeffrey and Williams [29]
Male ddY mice	glandular stomach, colon, liver, kidney, urinary bladder, lung, brain, and bone marrow comet assay	+ (glandular stomach and colon)	Sasaki *et al.* [30]
Salmonella typhimurium	Ames	-	Bandyopadhyay *et al.* [31]
Swiss albino mice	Comet assay	+	Bandyopadhyay *et al.* [31]
Fish sperm DNA	DNA binding affinity	+/-	Icsel and Yılmaz [32]
Human leukocytes	Alkaline and neutral comet assays	-	Frenzilli *et al* [33]

Footnote: + (Positive), - (Negative)

TABLE 2 -Sum of the carcinogenicity of saccharin in animal models.

Test material	Carcinogenicity model	Results	Reference
Male and female Charles River rats	Bladder tumors	-	Munro *et al.* [34]
	Bladder tumors	+	Howe *et al.* [16]
Rats and mice	Bladder tumors	+	Reuber [37]
	Bladder tumors	-	Risch *et al.* [35]
	Bladder tumors	-	Morgan and Wong [36]
Rats	Bladder tumors	+	Cohen *et al.* [39], Zurlo and Squire [38], Andreetta *et al.* [19]
Monkey	Bladder tumors	-	Takayama *et al.* [40]

Footnote: + (Positive), - (Negative)

TABLE 3 - Sum of the carcinogenicity of saccharin in epidemiological studies.

Study design	Carcinogenicity model	Results	Reference
Human	Bladder	-	Armstrong and Doll [41]
Human	Bladder	-	Jensen and Kamby [42]
1953 cases and 4154 controls	Colorectum	-	Francheschi *et al.* [46]
254 bladder cancer patients and 254 Controls	Bladder	+	Yu *et al.* [43]
598 cases and 1491 controls	Oral cavity and pharynx	-	Francheschi *et al.* [47]
304 cases and 743 controls	Oesophagus	-	Bosetti *et al.* [48]
1031 cases and 2411 controls	Ovary	-	Bosetti *et al.* [49]
460 cases and 1088 controls	Larynx	-	Bosetti *et al.* [50]
2569 cases and 2588 controls	Female breast	-	Tavani *et al.* [51]
1294 cases and 1451 controls	Prostate	-	Bosetti *et al.* [52]
767 cases and 1534 controls	Renal cell	-	Bravi *et al.* [53]
51 patients and 87 controls	Urinary tract	+	Andreatta *et al.* [19]
230 patients and 547 controls,	stomach	-	Bosetti *et al.* [54]
326 patients and 652 controls	pancreas	-	Bosetti *et al.* [54]
454 patients and 908 controls	endometrium	-	Bosetti *et al.* [54]

Footnote: + (Positive), - (Negative)

longevity in male rats. Howe *et al.* [16] reported a significantly increased risk for bladder cancer among saccharin consumers. However, the work of Risch *et al.* [35]) and Morgan and Wong [36] did not confirm this finding. Reuber [37] reported that saccharin is carcinogenic for the urinary bladder in rats and mice, and most likely is carcinogenic in human beings. The neoplasms of the urinary bladder are malignant, invade and metastasize. Male rats are more susceptible to urinary bladder carcinogenesis than female rats. Even though carcinomas of the urinary bladder are present in rats given the higher doses of saccharin, one was observed in a female rat given 0.5%. Experimental studies show also that sodium saccharin induces calcium phosphate precipitates in rat urine, which causes irritation, hyperplasia and, ultimately, tumors [19, 38, 39]. Takayama *et al.* [40] investigated the sodium saccharin (25 mg/kg) carcinogenicity on 20 monkeys, for up to 24 years. Authors have reported that none of the animals developed bladder cancer or urothelial proliferations.

3.3 Epidemiological works

Armstrong and Doll [41] analyzed 19 709 deaths in view of the bladder cancer mortality in the UK, between 1966 and 1972. They compared between artificial sweetener users and non-users. Authors reported that there were no significant differences between the groups. Jensen and Kamby [42] studied the cancer mortality in people who were born between 1941 and 1945. There was no significant increase in bladder cancer. Yu *et al.* [43] conducted a case–control study in 254 bladder cancer patients and 254 controls in China. They reported that, compared with non-users, by the use of saccharine for more than 19 times per year, and for more than 15 years, significant associations were found. Statistically significant associations were also found for diseases related to the urinary system. Goodman *et al.* [44] reported that there was no association for saccharin consumption and renal cell carcinoma in 267 patients. Gallus *et al.* [45] analysed artificial sweeteners (including saccharin) and cancer incidence works conducted in Italy between 1991 and 2004, with 1953 colorectum cancer cases and 4154 controls {45, 46], 598 oral cavity and pharynx cancer cases and 1491 controls [45, 47], 304 oesophagus cancer cases and 743 controls [45, 48], 1031 ovary cancer cases and 2411 controls [45, 49], 460 larynx cancer cases and 1088 controls [45, 50], 2569 female breast cancer cases and 2588 controls [45, 51], 1294 prostate cancer cases and 1451 controls [45, 52], and 767 renal cell carcinoma cases and 1534 controls [45, 53]. Authors have reported that there is no evidence about the increased risk of cancer and saccharin consumption at several common sites in humans.

Andreatta *et al.* [19] studied the correlation between the urinary tract tumors (UTT) and artificial sweetener use. 51 UTT patients and 87 controls used artificial sweeteners (including saccharin). Authors have reported that the risk of UTT was significantly increased in long-term (≥10 years) artificial sweetener users, compared with none- artificial sweetener users. Bosetti *et al.* [54] investigated a case control study with 230 patients, histologically confirmed cancers of the stomach and 547 corresponding controls, 326 of the pancreas and 652 controls, and 454 of the endometrium and 908 controls. The authors reported that saccharin consumption is not associated with the risk of cancer of the stomach, pancreas, and endometrium.

4. CONCLUSION

In conclusion, according to the literature on genotoxicity and carcinogenity of saccharine is still confusing. So, consumers should be careful to the consumption of this artificial sweetener.

The authors have declared no conflict of interest.

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CORRESPONDING AUTHOR

Serkan Yilmaz
Ankara University
Faculty of Health Sciences
Department of Midwifery
Aktaş Kavşağı Altındağ
Ankara, 06340
TURKEY

E-mail: syilmaz@health.ankara.edu.tr