



Toxicological Aspects of Saccharin

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Abstract

Saccharin is a widely used sweetener especially prescribed for the diabetics. But since its discovery, its use has been a matter of controversy due to its tumour promoting abilities in second generations of rats. As a result, saccharin was thought to be unfit for human consumption. Later on various studies focused on the possible mechanism of carcinogenic effects of saccharin on different animals. Several epidemiological studies were conducted to find out the relation of saccharin with cancer promotion. But no significant association was found between saccharin intake and cancer in humans. It was found that urinary bladder cancer is a high dose phenomenon and is species specific, which occurs only in rats. Lastly, in 2000, saccharin was removed from the list of human carcinogens by National Toxicology Programme, USA and International Agency for Research on Cancer (IARC). In this article, an effort has been made to study the historical and toxicological aspects of saccharin.

Keywords: *Saccharin, carcinogenicity, bladder cancer, food additive, sweetener, sodium saccharin.*

INTRODUCTION

Saccharin (CAS No. 81-07-2) is a non-caloric food additive known for its sweetness. Its molecular formula is $C_7H_5NO_3S$. This chemical is one of the most extensively studied and investigated in relation to its possible carcinogenic effects. Saccharin is a heat stable chemical with a long shelf life and is inexpensive. Because of its sweetness, which was glucose free, it was originally thought to be used for diabetic patients as an alternate source of sugar. In areas with shortage of sugar, it proved to be a boon. Apart from being used as a sweetener, saccharin is used for different purposes including as an antiseptic, antistatic agent, preservative, nickel plating etc. [1]

Saccharin use remained a controversy due to its carcinogenicity in rats. But it attained the 'generally recognized as safe' (GRAS) status in 1958. In 1970, a positive association was found between saccharin and bladder cancer in two generation bioassay in rats. Later, in 1973, Hicks *et al.* [2] wrote a letter in Nature about the carcinogenic effect of saccharin in chemical induction of bladder cancer. This was followed by a research paper, again by Hicks *et al.* [3] titled "Impurities in saccharin and bladder cancer." These studies again put saccharin in controversy for its possible ability to induce urinary bladder neoplasms in rats.

TOXICOLOGICAL STUDIES ON SACCHARIN

In 1974, Armstrong and Doll [4] reported bladder cancer mortality

in England in relation to saccharin consumption. Armstrong and Doll [5], in another study in 1975, investigated bladder cancer mortality in diabetics in relation to saccharin consumption. They investigated the death certificates of 18,733 patients who died from bladder cancer with diabetes mellitus. Diabetics were found to consume more saccharin than non-diabetics. But this study found no relation of diabetes of long duration with increased bladder cancer risk. In 1977, Culliton [6] wrote an article titled "Cancer society takes pro-saccharin stand" thus increasing the saccharin controversy. In 1978, many researchers started investigating and writing about the possible carcinogenicity of saccharin [7-12]. In 1979, Cohen *et al.* [13] reported saccharin as a potent promoting agent of bladder tumours having a short latent period in male Fischer rats. Meneely [14] in 1979, wrote on "Saccharin and cancer." Hooson *et al.* [15] in 1980, reported the carcinogenicity of saccharin and ortho-toulene sulphonamide (OTS) in rats. This study did not find any tumour promoting abilities but reported an increase in the proliferative lesions in the rat urinary bladders. Similarly, Nakanishi *et al.* [16] reported the induction of early stage bladder lesions due to saccharin with a dose responsive effect in Fischer 344 rats. On the contrary, Schmahl and Habs [17] gave a clear chit to saccharin reporting that the application of cyclamate and saccharin during pregnancy do not pose a risk for any type of cancer risk in sprague-dawley rats. Thus, the controversy persisted.

SACCHARIN RESEARCH: THE POSSIBLE MECHANISMS

Till 1980, many studies had reported for the carcinogenicity of saccharin, but at that time, its mechanism was not known. In 1981, Kakizoe *et al.* [18] demonstrated the possible mechanism by which saccharin causes its cancer promoting effect. This study reported that saccharin, when given continuously, maintained an increased agglutinability of isolated bladder epithelial cells of rat, resulting in tumour promoting effects. Various animal experiments till then, had shown a carcinogenic effect of saccharin on rats. It was proved that rats fed on saccharin were more prone to develop bladder tumours if they have been exposed to saccharin in-vitro through their mother's

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food. There was no evidence of bladder tumour risk in humans following in-utero exposure to saccharin. In 1982, Jensen and Kamby [19] investigated intra-uterine exposure to saccharin and risk of bladder cancer but found no evidence of human bladder cancer risk in the first 30-35 years of life in relation to in-vitro saccharin exposure. After reports on bladder cancer, Pereira *et al.* [20] reported the tumour promoting ability of saccharin in rat liver. This study reported the induction of hyperplastic nodules and hepatocellular carcinoma with the administration of sodium salt of saccharin in the diet with Di-butyl nitrosamine (DBN). Saccharin proved to increase the tumourigenic response of DBN in liver.

Again in 1983, Renwick and Sims [21] reported the bladder distention ability of saccharin in rats. Short term administration of high dietary levels of saccharin used in previous two generation cancer bioassays, produced functional changes in urinary bladder. Higher incidences of tumours were also reported. These reports awakened the researchers to find out more about the possible mechanisms of tumour induction by saccharin as Kakizoe *et al.* [18] did in 1981. In 1984, Byard and Clayson [22], in two different studies, worked on the possible action mechanism of saccharin. Clayson [23] suggested that saccharin is associated to bladder cancer due to its relation with the integrity of the urothelial permeability barrier in Sprague-Dawley rats. It was also suggested that once saccharin enters the urothelium, it inhibits certain enzymes, resulting in the ultimate effect. To further enhance the study on saccharin, Hasegava *et al.* [24] in the same year investigated the possibility of a mutagen being generated as a result of saccharin feeding. No bacterial contamination, production of nitrosamines or mutagenic activity was found in urine of sodium saccharin fed rats. As to study the effect on liver, in line with Pereira *et al.* [20], no significant changes in liver microsomal enzymes (cytochrome p-450, NADPH cytochrome C reductase and aniline hydroxylase) were observed following sodium saccharin feeding. Agglutination of rat urinary bladder epithelial cells by concanavalin A (Con A) had been earlier reported by Kakizoe *et al.* [18]. On the same track, Suzuki *et al.* [25] in 1984, reported that Con A distinguishes between regeneration hyperplasia induced by cyclophosphamide (CP) or freezing, followed by sodium saccharin in the diet and results in bladder cancer in rats.

Thus, the reports related to the carcinogenicity of saccharin put a mark on the use of saccharin for human consumption. Even, the results of studies on rats, hamsters, mice and monkeys for saccharin carcinogenicity were positive in the second generation only as compared to the control animals. The studies had not reported saccharin as a cancer inducer in a single generation. In 1985, Council on Scientific Affairs [26], reviewed the safety issues of saccharin in relation to human consumption. As available evidences indicated no association of saccharin with the induction of bladder cancer in humans, the council suggested that saccharin should continue to be available as a food additive for human consumption although adverse health effects should be monitored. In 1985, many studies were conducted to find more on the toxicological aspects of saccharin [27-33]. Armstrong [27], in an epidemiological survey in 1985, failed to find any evidence of an increase in bladder cancer risk in diabetics using more saccharin than non-diabetics. At that time, the literature available indicated that sodium salt of saccharin is non-reactive to DNA and inactive as a gene mutagen in-vitro. The recorded genotoxic activity of these salts became apparent only at elevated dose levels. Thus, Ashby [28] stressed upon the need to

evaluate the genotoxicity of potassium, calcium and sodium salts of saccharin.

Parallel studies in 1985 on effects of saccharin on man were going on. In this light, Carlborg [29] concluded that cancer risk at low doses of saccharin on man is very small. In 1986, Cohen [34] reported that epidemiological studies in human beings have not found an increased risk of developing bladder cancer with exposure to saccharin. In an another study, Gaylor *et al.* [35] estimated the upper limit of bladder cancer risk to be between 0.00038 and 0.18 times the percentage of saccharin in the diet. In 1990, Ellwein and Cohen [36] reported that the chemical form of saccharin in the urine is unaffected, and there is no evidence for a specific cell receptor for the saccharin molecule. Changes in several urinary parameters, such as pH, sodium, protein, silicates, volume, and others, appear to influence the reaction of the urothelium to sodium saccharin administration. Next year, in 1991, Homma *et al.* [37] indicated no demonstrable bladder carcinogenicity of sodium saccharin in analbuminaemic rats. Similarly, Okamura 1991 [38] demonstrated that sodium saccharin does not promote bladder cancer in male rats if fed in AIN-76A diet. Carcinogenic effects were again reviewed by Chappel [39] in 1992 showing that saccharin does not increase the risk of bladder cancer in humans and laboratory investigations have shown that sodium saccharin is not mutagenic and does not bind to DNA. Renwick [40] in 1993, demonstrated that the toxic effect of saccharin is only seen under specific conditions in rats, largely with the sodium salt and with a commercial rat diet. The effect is not related to the concentration of saccharin in the rat urine or bladder. Since then, many other researches were done on saccharin use [41-45]. In 2000, in the absence of concrete evidence against carcinogenicity of saccharin in humans, the National Toxicology Program (NTP), USA, removed saccharin from its report on carcinogens. Also, the International Agency for Research on Cancer (IARC) changed its rating of saccharin from Group 2B, "possibly carcinogenic to humans" to Group 3, "not classifiable as to the carcinogenicity to humans".

CONCLUSION

Since its discovery in 1879, saccharin remained in controversy regarding its fitness for human consumption. The studies on rats have demonstrated its ability to produce bladder cancer in two generation bioassays. Now, this fact has been accepted worldwide that saccharin is cancerous in rats in high doses and saccharin does not pose a risk of cancer in human beings and can be continued to be used as a food additive.

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