

Artificial sweeteners—do they bear a carcinogenic risk?

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Artificial sweeteners are added to a wide variety of food, drinks, drugs and hygiene products. Since their introduction, the mass media have reported about potential cancer risks, which has contributed to undermine the public's sense of security. It can be assumed that every citizen of Western countries uses artificial sweeteners, knowingly or not. A cancer-inducing activity of one of these substances would mean a health risk to an entire population. We performed several PubMed searches of the National Library of Medicine for articles in English about artificial sweeteners. These articles included 'first generation' sweeteners such as saccharin, cyclamate and aspartame, as well as 'new generation' sweeteners such as acesulfame-K, sucralose, alitame and neotame. Epidemiological studies in humans did not find the bladder cancer-inducing effects of saccharin and cyclamate that had been reported from animal studies in rats. Despite some rather unscientific assumptions, there is no evidence that aspartame is carcinogenic. Case-control studies showed an elevated relative risk of 1.3 for heavy artificial sweetener use (no specific substances specified) of >1.7 g/day. For new generation sweeteners, it is too early to establish any epidemiological evidence about possible carcinogenic risks. As many artificial sweeteners are combined in today's products, the carcinogenic risk of a single substance is difficult to assess. However, according to the current literature, the possible risk of artificial sweeteners to induce cancer seems to be negligible.

Key words: aspartame, cancer, cyclamate, saccharin, sweeteners

Introduction

The fondness of humans for sweet foods is inborn: studies have proved a preference for sweet-tasting nutrition in newborns [1]. Therefore, mankind has always added sweet substances to their food. The first recorded sweetener was honey, which was used in the ancient cultures of Greece and China [2]. Honey was later replaced by saccharose, common sugar, which was originally obtained from sugar cane. During the World Wars, sugar beets were the major source of saccharose. The first artificial sweetener was saccharin, which was synthesized in 1879 by Remsen and Fahlberg. It was well accepted during World Wars I and II because of its low production costs and the shortcoming of regular sugar [2]. As economies recovered and living standards increased after the wars, sugar became affordable. With a growing candy and fast food industry, obesity increased in the Western societies, as we know today from our daily clinical practice. Since the 1950s, the reasons for using saccharin have shifted from cost to calorie reduction. A profitable market for calorie-reduced 'diet products' evolved, in which sugar was substituted or

supplemented with artificial sweeteners. However, saccharin was known not only for its extreme sweetness, but also for its bitter aftertaste, so that there was a growing need for new improved taste, calorie-reduced substances. A breakthrough in the artificial sweetener industry was achieved with cyclamate in the 1950s, which provided a better taste than saccharin. In addition, it blended very well with saccharin. Both substances were mixed together with other additives and were sold as 'Sweet'n'Low', which became a huge success in the USA. Because of its characteristics, cyclamate was not only used in tablet or liquid form ('table top sweetener'), but also proved suitable for sweetening soft drinks.

The first insecurity shook the artificial sweetener market in 1970, when the Food and Drug Administration (FDA) banned cyclamate from all dietary foods and fruits in the USA. The FDA had become suspicious of induced cancer in experimental animals [3]. In all other countries, cyclamate is still used today, especially in combination with other sweeteners. The next step in the development of artificial sweeteners was the approval of aspartame in 1981 and its marketing as 'Nutra-Sweet'. For the first time, dairy products such as yogurts were calorie-reduced and could be sold with the prefixes 'diet' or 'light' [4]. The first three substances, saccharin, cyclamate and aspartame, are referred to as 'first generation sweeteners'. These were followed by new generation or second generation sweeteners such as acesulfame-K, sucralose, alitame

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Table 1. Current artificial sweeteners and their key market areas (taken from Lindley [4])

Sweetener	Key market areas
Acesulfame-K	North America, Europe and Asia
Alitame	Oceania, South/Central America
Aspartame	North America, Europe and Asia
Cyclamate	Europe and Asia
Neohesperidine DC	Europe and Japan
Neotame	USA
Saccharin	Asia, Europe and USA
Stevioside	Asia
Sucralose	North America
Thaumatin	Europe and Asia

and neotame, which have quite different key market areas, as shown in Table 1 (from Lindley [4]). However, even the new sweeteners have similar limitations to the older ones. The taste is often accompanied by a bitter and metallic aftertaste and does not provide the 'realistic' and 'voluminous' mouth-feel of regular sugar. The combination of many, synergic artificial sweeteners has led to an improvement of the quality of sweetened products. In soft drinks, a combination of acesulfame-K, aspartame and others has found broad application (as shown in Figure 1).

Today, many people have mixed feelings when using artificial sweeteners, because they associate news about possible cancer risks with these substances. Particularly in the 1980s, when many sweeteners were newly synthesized and introduced to the food market, the public press reported on the ostensible carcinogenic effects of sweeteners. News articles frequently lacked a fundamental scientific background or were inattentively investigated, and added to a public insecurity. Even some of the scientific publications in reliable medical journals, which caught media attention, were not well researched, and ignored common statistical knowledge as

described later. During the last decade, the cancer-inducing effect of artificial sweeteners has not been discussed as frequently as in earlier years, although some of the long-term studies about saccharin and cyclamate have recently been completed and published.

Methods

Several PubMed searches of the National Library of Medicine were performed. Relevant preclinical, clinical and epidemiological studies on artificial sweeteners and possible health risks were identified. All searches focused on English language journals only, but were not limited to a certain period of time. Where appropriate, cited references of articles were also reviewed. Key words for the PubMed search included 'artificial sweetener', 'cancer' and 'carcinogenic', as well as all artificial sweetener names. To present an overview, the studies were sorted by the investigated artificial sweetener, and will be discussed separately.

Results

Saccharin

Saccharin is the oldest chemical sugar substitute and the best researched of all sweeteners. More than 50 studies have been published about saccharin in laboratory rats. Approximately 20 study groups analyzed the effect of saccharin in one generation of rats, which were exposed to high doses of saccharin for at least 1.5 years. Usually, the doses administered included a high concentration of 5% of the various forms of saccharin in the diet, and in several cases, animals started the study at 6 weeks of age. Except for one study, none of the 20 groups found significantly more neoplasias in the saccharin-fed animals than in controls. The positive study reported an increased incidence of bladder cancers [5]. However, ACI rats were used in this trial, which are frequently infected with the bladder parasite *Trichosomoides crassicauda* and are therefore susceptible to saccharin-induced bladder cell proliferation [6].

After many 'one generation' studies, 'two generation' studies were conducted feeding the parent (F₀) and the following

VERY LOW SODIUM		
Nutrition Facts	Amount/Serving	% DV*
	Total Fat 0g	0%
Serv. Size 8 fl oz (240 mL)	Sodium 30 mg	1%
Servings 2.5	Total Carb 0g	0%
	Protein 0g	
Calories 0	*Percent Daily Values (DV) are based on a 2,000 calorie diet.	
CARBONATED WATER, CARAMEL COLOR, ASPARTAME, PHOSPHORIC ACID, POTASSIUM BENZOATE (TO PROTECT TASTE), NATURAL FLAVORS, CITRIC ACID, CAFFEINE.		
PHENYLKETONURICS: CONTAINS PHENYLALANINE		

A

Kalorienarmes, koffeinhaltiges Erfrischungsgetränk mit Pflanzenextrakten, mit Süßungsmitteln	
Zutaten: Wasser, Kohlensäure, Farbstoff E 150d, Süßstoffe [Natrium-cyclamat, Acesulfam-K, Aspartam (enthält eine Phenylalaninquelle)], Säuerungsmittel Phosphorsäure und Citronensäure, Aroma, Koffein.	
Nährwertangaben je 100 ml:	
Brennwert	<1,0 kJ (<0,25 kcal)
Eiweiß	<0,1 g
Kohlenhydrate	<0,1 g
Fett	0 g

B

Figure 1. Two product labels of a diet soda, taken from the USA (A) and Germany (B). In the USA, only aspartame is used in this soda, whereas the same product is sold in Germany with an artificial sweetener combination of cyclamate, acesulfame-K and aspartame.

generation (F₁) with saccharin. In these studies, an increased risk for bladder cancer could be consistently proven for the F₁ generation. Taylor et al. [7] showed that especially male rats developed bladder tumors in up to 30% of all animals at a dose of 7.5% saccharin of their diet. Later trials, the largest with 2500 F₁ generation rats [8], found that the risk for bladder cancers increases with a saccharin concentration of 4%. Because of these results, saccharin was prohibited in Canada. In the USA, since 1981, saccharin-containing products have had to be labeled with a warning that saccharin can cause cancer in laboratory animals. However, the National Institute for Environmental Health Sciences, which issues a biannual report, removed saccharin as a potential cancer-causing agent, because it could be shown that the cancer-inducing mechanisms in rats do not apply in humans. Ascorbic acid (vitamin C), when fed in similar doses as saccharin, could also cause bladder cancer in rats; this could be prevented by adding prophylactic ammonium chloride. Rodents have a high urine osmolarity, which enhances the precipitation of calcium phosphate-containing crystals, which are cytotoxic to the superficial layer of the bladder epithelium, leading to regenerative hyperplasia and tumors [9].

Takayama et al. [10] in 1998 published a long-term study on 20 monkeys, of three species, that were treated with sodium saccharin (25 mg in the diet/kg daily for 5 days a week) for up to 24 years. Sixteen monkeys served as controls. None of the animals developed bladder cancer or urothelial proliferations. The study was criticized for the small number of monkeys and for the relatively low dosage of saccharin, which corresponds to a daily diet-soda consumption of 1.5 l in a 70-kg person [11]. The first studies about the cancerogenous risk of saccharin in humans were only of descriptive design. In the UK, a longitudinal study did not show an increase in bladder cancer incidence during World War II, when saccharin consumption was high [12]. The same authors analyzed 19 709 death certificates from the UK between 1966 and 1972 and compared the bladder cancer mortality between diabetics, who used artificial sweeteners more frequently, and non-diabetics. They did not find any significant differences between the groups [13]. A Danish study could not detect an increase of bladder cancer mortality in people aged up to 30 years old, who were born between 1941 and 1945, when saccharin use was higher than in the years before and after [14]. The authors concluded that an exposition to saccharin *in utero* does not increase bladder cancer incidence during the first three decades of life. A case-control study from China published in 1997 analyzed different risk factors in 254 bladder cancer patients and 254 controls [15]. They reported an odd ratio of 3.9 for bladder cancer in patients with frequent saccharin use of at least 19 consumptions per year for at least 15 years. However, this study has to be critically assessed as to its worth, because it was unable to identify the elevated risk of bladder cancer in smokers, which was proven by other large trials [16–18]. There are many case-control studies from the USA and Europe about bladder cancer risk factors, which not only investigate saccharin as a possible cause, but

also the use of artificial sweeteners in general. Therefore, they will be discussed later in this review.

Cyclamate

Sodium cyclamate entered the US market after its FDA approval in 1951 [19]. Owing to a study by Wagner in 1970 [20], which found an increased incidence of bladder carcinomas in rats, the use of cyclamate was prohibited in several countries, including the USA and UK. Further evaluations by the Cancer Assessment Committee of the Center for Food Safety and Applied Nutrition of the FDA, by the Scientific Committee for Foods of the European Union and by the WHO concluded that cyclamate is not a carcinogen, and readmitted it to the food market [21].

Cyclamate is converted to a metabolite, cyclohexylamine, which has been reported to be rather toxic [22]. In experiments with rats and dogs, cyclohexylamine caused testicular atrophy and impairment of spermatogenesis [23–26]. Takayama et al. [21] conducted a long-term toxicity study with cyclamate in non-human primates, as described before for saccharin. Twenty-one monkeys were fed either 100 or 500 mg/kg cyclamate per day over 24 years, and compared with 16 controls. A dose of 500 mg/kg corresponds to ~30 calorie-reduced drinks. In 1994, after 24 years, the remaining 14 cyclamate and 16 control monkeys were killed and autopsied. In the cyclamate group, three animals showed malignancies, whereas none were found in the controls. The tumor stages and histologies of the cancers were a metastatic adenocarcinoma of the colon (500 mg/kg), a metastatic hepatocellular carcinoma (500 mg/kg) and a local well-differentiated papillary adenocarcinoma of the prostate (100 mg/kg). In addition, three benign tumors were found in the treatment group, an adenoma of the thyroid gland and two leiomyoma of the uterus, whereas the control group remained free of tumors. The authors concluded that there is no evidence for carcinogenicity of sodium cyclamate, because the tumors in the treatment groups were of different histologies and the tumors occurred at a rate frequently observed in monkeys. In particular, no bladder carcinomas were reported as in the rat study, which had led to the ban of cyclamates. The trial of Takayama et al. [21] was criticized for the small number of animals, which was too low to reach any significance or to confirm a negative result [27]. In addition, the critics claimed that the tumor incidence in the treatment group (33%) was higher than the spontaneous neoplasia rate in respective monkey strains, and unlikely to be a chance occurrence. There are no descriptive or case-control studies of cyclamate in humans, because it was approved after saccharin, and products contained mixtures of both artificial sweeteners. It has to be assumed that most consumers have used both saccharin and cyclamate since the introduction of cyclamate.

Aspartame

Aspartame entered the market in 1981 as the third artificial sweetener, and was free of any suspicions regarding

carcinogenicity. Animal studies showed that aspartame does not have any cancer-inducing effects, even in very high doses [28, 29]. DNA repair assays for the evaluation of genotoxicity of substances did not show any DNA-damaging properties for aspartame, cyclamate, saccharin, acesulfame-K or sucralose [30]. Fifteen years after the approval of aspartame, the *Journal of Neuropathology and Experimental Neurology* published an article by Olney et al. [31] with the title ‘Increasing brain tumor rates: Is there a link to aspartame?’, which received tremendous attention from the mass media, as well as the scientific community. The authors hypothesized that the increasing rate of brain tumors in humans since 1980 could possibly be explained by the introduction of aspartame. They supported their hypothesis with an FDA trial in 320 Sprague–Dawley rats. Twelve rats developed malignant brain tumors after receiving an aspartame-containing feed for 2 years [32]. They argued that another trial had shown that the aspartame molecule acquires mutagenic activity when nitrosated [33]. The publication of Olney et al. [31] led to heavy criticism of the scientific community, whereas the laymen press suggested abstaining from aspartame-sweetened products [34]. In an editorial, Ross [35] demonstrated the weaknesses of the Olney study. He explained that Olney et al. [31] linked two events that incidentally occurred during roughly the same time period: the increase of brain tumors and the introduction of aspartame. This correlation is not admissible in epidemiology, and is called ‘ecological fallacy’. There was no information available regarding whether the individuals who developed brain tumors consumed aspartame. As Ross states, one might also invoke home computers, VCR usage or the depletion of the ozone layer to argue trends in brain tumors. In addition, the introduction of aspartame and the rising brain tumor rate occurred almost simultaneously. For the development of brain tumors, a certain latency would have been required. The study that showed an increased brain tumor incidence in aspartame-fed rats, which gave rise to the argument of Olney et al., could not be confirmed by later trials [36]. Ross [35] suggested evaluating the link between aspartame exposure and brain tumors in a case–control or cohort study.

Indeed, a case–control study on aspartame consumption was conducted in children with brain tumors [37]. The study group compared 56 patients with 94 controls in terms of aspartame use and other known and suspected risk factors, such as maternal vitamin consumption, cured meat intake, passive smoke exposure, X-ray exposure and family history of brain cancer. They observed no elevated brain tumor risk to the child from maternal consumption of aspartame during pregnancy, nor did they find elevated risks during any trimester of pregnancy or during breast-feeding. After the questionable study of Olney et al. [31], Schwartz [38] wrote a letter to the *Western Journal of Medicine*, which was published in 1999. Schwartz hypothesized a link between aspartame and the increase of breast cancer. He argued that aspartame is partly metabolized to methanol, which itself is converted to formaldehyde, which accumulates within cells and induces cancer [39]. In the same issue of the journal, Tichopoulos [40] responded to the letter.

He explained that the increase of the breast cancer rate occurred before the introduction of aspartame, and has been declining during the last few years [39, 41]. He concluded that Schwartz also succumbed to an ecological fallacy.

New generation sweeteners

Except for the toxicological animal data required for FDA approval, there are no larger studies that investigate the potentially hazardous effects of second generation sweeteners. None of the substances such as acesulfame-K, neohesperidine, alitame or sucralose has been suspected to cause cancer or to be genotoxic.

Epidemiological studies in humans

After cyclamate and aspartame had entered the food market, diseases such as bladder cancer could not be linked to the consumption of saccharin alone, because most consumers used different artificial sweeteners. Also, substances were mixed in food products to improve the taste. Therefore, most epidemiological studies in humans relate to sweetener consumption in general, and not to single substances. The most important publications in this field are case–control studies. Many of these trials were conducted with small patient groups of up to 350 bladder cancer patients in the years 1965–1986 [42–46]. None of them showed a significantly increased risk of bladder carcinoma for artificial sweetener use. A study from the UK [47] included 622 existing and 219 new cases of bladder cancer, and matched them to hospital-based controls for age and sex. The study group found an increased relative risk (RR) for non-smoking males [RR 2.2; 95% confidence interval (CI) 1.3–3.8] and non-smoking females (RR 1.6; 95% CI 0.8–3.2), but not for smokers. Sweetener use was defined as regular use for over 1 year at least 5 years prior to diagnosis.

The most recent case–control study was published by Sturgeon et al. [48] with 1860 bladder cancer patients and 3934 controls. They examined different factors, among which were smoking, urinary tract infection, coffee consumption, history of cystolithiasis and genetic predisposition for the risk of inducing bladder cancer. Artificial sweetener consumption was classified as ‘low’ (<1680 mg per day) or ‘heavy’ (>1680 mg per day). The risk of bladder cancer was not associated with low sweetener use in 966 patients and 3410 controls. Heavy sweetener consumption (31 patients, 78 controls) led to a significantly increased RR of 1.3 (95% CI 0.9–2.1). Also, high coffee consumption of >50 cups per week was associated with an RR of 1.4, and therefore was comparable to heavy artificial sweetener use or the history of one to two urinary tract infections (RR 1.3). The authors scrutinized the bladder cancer histologies. Heavy artificial sweetener use was associated with higher grade, poorly differentiated tumors.

Conclusions

Owing to the existing studies, the following statements can be made about the carcinogenic potential of artificial sweeteners.

Saccharin induces bladder cancer in rats, when fed in high doses. However, rodents react to most sodium salts, such as sodium ascorbate, with urothel proliferation and neoplasia of the bladder.

Heavy artificial sweetener use (>1680 mg per day) leads to an increased relative risk of 1.3 for bladder cancer in humans. A more precise determination of the exact agents is not possible, because many artificial sweeteners are combined in current food products.

Despite unscientific articles in the mass media and scientific press, there is no evidence that the artificial sweetener aspartame bears a carcinogenic risk.

The approvals of new generation sweeteners (acesulfame-K, sucralose, alitame and neotame) are too recent to establish any epidemiological evidence about possible carcinogenic risks.

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