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THE CARCINOGENIC EFFECTS OF ASPARTAME Devora Sara Gelbfish

Abstract

Aspartame, one of the most common artificial sweeteners, is used as a food additive worldwide. Because of early experimentation with rats linking aspartame to higher risk of cancer, there is much concern regarding the safety of aspartame. However, analytical review and numerous subsequent studies have disproven previous experimentation and reaffirmed that aspartame consumption in humans does not increase the risk of cancers. At the current time there is no credible evidence to support the idea that aspartame is carcinogenic. The evidence confirms that at current levels of consumption aspartame is a safe alternative to sucrose.

Introduction

In recent years artificial sweeteners have become more and more popular as consumers continue to seek alternatives to regular table sugar that offer sweetness without calories. Because artificial sweeteners contain virtually no calories, they can be very effective in aiding weight control. Additionally, artificial sweeteners like aspartame are useful to diabetics because they are not carbohydrates, and therefore, do not raise blood sugar. Instead, aspartame is broken down into its constituent amino acids and incorporated into normal metabolism without impacting blood sugar levels (Renwick 1986).

However, the safety of artificial sweetener consumption has been debated for years due to early studies linking them to incidents of cancer. Despite the fact that these studies were later overturned, concern about the long-term deleterious effects of artificial sweeteners remains strong.

On the one hand, excess sugar consumption is unhealthy. The prevalence of obesity and diabetes is rising at alarming rates, leading to numerous health problems. On the other, with the increase in consumption of artificial sweeteners, are we putting ourselves at risk for cancer? Unfortunately, so many studies have been conducted only later to be overturned, leading to much confusion in the area of artificial sweeteners. Many consumers avoid artificial sweeteners because they believe that the "chemicals" are hazardous to their health or because they have read headlines linking aspartame to cancer. However, are those claims backed by scientific data? Is it all just publicity and hysteria, or is aspartame truly carcinogenic?

History of Aspartame

Aspartame is formally known as L- α -aspartyl-L-phenylalanine methyl ester. (Figure 1) Commonly known by the brand names Equal and NutraSweet, aspartame was accidentally discovered in 1965 by a scientist who was working on the synthesis of a gastrointestinal secretory hormone inhibitor. While working in the lab, some solution was accidentally spilled and splashed on his hand. Soon afterwards, against all good safety practices, he licked his finger to pick up a piece of paper and was shocked by the intense sweetness of the aspartame that had been splattered there (Magnuson et al. 2007).

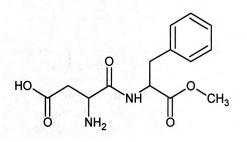


Figure 1. Structure of aspartame $(L-\alpha-aspartyl-L-phenylalanine methyl ester).$ (Magnuson et al. 2007)

Aspartame was originally proposed for approval in the United States in 1974, but it was not until 1981 that it was approved for dry products. Finally, in 1983 it was further approved for use in drinks and subsequently all foods (European Food Safety Authority 2006). Then, in 1996, the safety of aspartame was questioned, once again, due to a report suggesting that aspartame consumption was responsible for an increase in brain tumors between 1975 and 1992. However, later studies and further analysis showed that the data did not establish a definite link between cancer development and aspartame consumption (National Cancer Institute 2009).

Trailing only saccharin, aspartame is the second most used artificial sweetener in the world. It is found in over 6000 kinds of products worldwide, among them soft drinks, chewing gum and candies. It has been used as a popular food additive for more than thirty years due to its intense sweetness which is about two hundred times the sweetness of sucrose. In the United States alone aspartame consumption is estimated at about 8000 tons per year. But, in the words of Soffritti et al. (2006), "[Aspartame's] ever-growing use…has been accompanied by rising consumer concerns regarding its safety, in particular its potential long-term carcinogenic effects."

The acceptable daily intake of aspartame is 40 mg/kg of body weight in Europe and 50 mg/kg body weight in the United States. Pharmacokinetic data in humans indicates that even when the full acceptable daily intake is taken at once, the aspartame is digested fast enough so that systemic exposure to aspartame never occurs. Moreover, it is important to note that current use levels, even by high users, remain well below the established acceptable daily intake levels. If all sucrose in the typical American diet was replaced with aspartame, the proposed estimated consumption would fall between twenty-two and thirty-four mg/kg of body weight per day. In more commonly relatable measurements, these amounts are equivalent to about fifty-seven packets of sweetener, or ten cans of diet soda, per day. In actuality, the most current data available shows that, on average, aspartame intake is 4.9mg/kg body weight per person per day (Stegink et al. 1981).

In rodents, pigs, nonhuman primates, and humans alike, aspartame is metabolized into aspartic acid, phenylalanine, and methanol in the gastrointestinal tract. Post-ingestion, the aspartame is hydrolyzed, resulting in the breakdown products listed above. After being absorbed into systemic circulation, the broken down compounds follow the metabolic pathways as they would if ingested through other foods. Aspartate and phenylalanine are used as amino acidic building blocks or transformed into alanine plus oxaloacetate and tyrosine, respectively, and partially into phenylethylamine and phenylpyruvate. The methanol is oxidized to become formaldehyde and then formic acid (Soffritti et al. 2006).

According to the European Food Safety Authority, "At doses relevant to human consumption hydrolysis is very efficient." All available evidence indicates that aspartame does not enter the bloodstream until after it is hydrolyzed. Consequently, it is important to bear in mind that studies in which aspartame was administered through injection, (thereby avoiding digestion,) "are not representative of oral administration, which is how aspartame is always consumed by humans" (Stegink 1987). Any cancers that resulted from systemic exposure to aspartame are not relevant to humans, since when ingested orally, aspartame is always broken down before entering systemic circulation.

Overview and Analysis of Original Studies Performed

From the time of its introduction by Searle Laboratories, aspartame has been surrounded by controversy. With the assistance of various scientists, Searle conducted hundreds of tests, summarized in Table 1 below, to ascertain the safety of aspartame as a food additive. Among the experimental works were studies conducted on rats, mice, hamsters, dogs, and monkeys. At the time, many felt that some important data was not reported to the Food and Drug Administration when Searle applied for the approval of aspartame. Ultimately, however, further analysis proved that none of the studies found evidence linking aspartame consumption to cancer.

In a 1996 report by Olney et al., the authors suggested that aspartame might be a cause of the increase in brain cancer in humans. From a descriptive analysis of national cancer data, they noted that the introduction of aspartame in food in the early 1980's corresponded to the rise in brain cancer in the United States. They recommended that the safety of aspartame as a sugar substitute be reevaluated.

Consequently, Gurney et al. performed a case-control study to assess the relationship of aspartame consumption and the risk of childhood brain tumors. They held in-person interviews with the biological mothers of their fifty-six case patients and ninety-four control subjects, collecting data on aspartame consumption prior to the date of diagnosis or reference date. The children were all born during or after 1981, corresponding to the Food and Drug Administration's approval of aspartame. In addition, for forty-nine case patients and ninety control subjects, the authors evaluated the risk of brain tumor as a result of the mother's aspartame consumption during pregnancy and breast feeding.

As a result of their studies the authors found that "case children were no more likely than control children to consume foods containing aspartame," and that "there was no suggestion of a dose-response relation based on age at first consumption, number of years of consumption, or frequency of consumption." Additionally, they found no correlation between maternal consumption of aspartame during pregnancy or breast feeding and increased risk of brain tumors (Gurney et al. 1997).

This study is informative; however, due to a number of weaknesses, it is not a strong enough proof to rule out the possibility that aspartame is linked to elevated risk of brain tumors. Firstly, much of the data was amassed through in-person interviews with the mothers of the case patients and control subjects, leaving lots of room for error as a result of biases. Aside from the

fact that no one has perfect recall, people also tend to lie or exaggerate information. Also, it is very possible that the interviewers asked leading questions and that the interviewees skewed the information in an attempt to provide what they thought the interviewers wanted to hear. Furthermore, the study sample was very small and may not have been an accurate representation of the full population. Finally, studies of children are naturally limited because one cannot study the effect of the possibility that the children who were exposed to aspartame consumption would have increased brain tumor risk as adults cannot be ruled out.

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				Treatment		Results	Conclusion(s) and statistical
Author	Test species	N	Dose (g/kg/day)	Duration	Endpoints	Dose g/kg Male Female	signincance (pvalue)
E72, Bryan (1984a, 1984b)	E72, Bryan (1984a, 1984b) Female Swiss albino mice	100/group	Bladder pellet ¹ with 0, 4.0 mg ASP, 4.0 mg DKP, or 4.0 mg XAE	26 weeks	Urinary bladder tumorigenicity with intravesical pellet implants	No statistically significant increase in any tumor type in treated groups as compared with control	Lack of increased tumors in positive control XAE group suggested insufficient
E72, Bryan (1984a, 1984b)	E72, Bryan (1984a, 1984b) Female Swiss albino mice	200/group	Bladder pellet with 0, 56 weeks 4.0 mg ASP, 4.0 mg DKP, or 4.0 mg	56 weeks	Urinary bladder tumorigenicity with intravesical pellet	Significant increase in bladder tumors in XAE-treated mice, but not in ASP or DKP treated mice	study duration ASP and DKP do not promote bladder tumors
Soffrititi et al. (2005, 2006) Sprague-Dawley rats.	Sprague-Dawley rats.	150/sex/dose for 0, 4, 20, and 100 mg/kg bw. 100/sex/dose for 500, 2500 and 5000 mg/kg bw	ASA	Lifetime until death	Implants Tumorigenicity when added to the diet at levels of 0, 80, 400, 2000, 10,000, 50,000 and 100,000 ppm	Increased in combined lymphoma/teukernia in females, renal carcinomas, mulignant schwarnomas of peripheral nerves	Authors conclude ASP has "multipotential carcinogenic effects". See discussion for conclusions by
Searle, E77/78 (1974)	Rats, Charles River (CD), Sprague-Dawley	36/sex/dose 72 control /sex	DKP = 0, 0.75, 1.5, 3.0	115 week	Brain tumors	0 (M+F) 2/123 (1.6)	expert reviews. No evidence of tumors due to compound.
Searle, E27 (1972a)	Hamsters	5/sex/dose	ASP = 1, 2, 4, 12	46 weeks	Neoplastic lesions	Lesions attributed to unidentified infection in colony. No turnors reported	NOAEL for DKP = 3 gkg/day No evidence of tumors due to compound; infection
Searle, E28 (1972b)	Dogs (purebred Beagles)	5/sex/dose	ASP = 0, 1, 2, 4	2 years	Physical exams every 4 weeks, periodic urine analysis, blood CBC and biochemical	No treatment related changes in body weight, food consumption, physical or clinical parameters, or postmortem examination	compromised study No evidence of toxicity. NOAEL for ASP = 4 g/kg/day
Promotional studies Ito et al. (1983)	Male F344 rats pretreated for 4 weeks with or without 0.01% BBN in water	Control group = 60, aspartame group = 36	0 or 5% ASP in diet. ASP was one of 16 test chemicals	36 weeks	Urinary bladder pathology	No difference between groups in incidence or severity of urinary bladder papillary or nodular hyperplasia	ASP does not promote urinary bladder papillary or nodular
Hagiwara et al. (1984)	Male F344 rats pretreated for 4 weeks with or without 0.01% BBN in water	25-30/group	0 or 5% ASP, stevioside, or saccharin in diet	32 weeks	Body weight, food, water, urine analysis, liver, kidney, and urinary bladder lesions	No abnormalities in rats treated with aspartame, stevioside or saccharin alone.	hyperplasia Saccharin, but not ASP, promoted bladder carcinogenesis NOEL = 5 g/kg/day

Table 1: Chronic Oral Toxicity Studies with aspartame and diketopiperazine (Magnuson et. al 2007)

Aspartame Consumption in Relation to Childhood Brain Tumor Risk: Results from a Case-Control Study

Nevertheless, there is one last important point that the authors did make. Given the fact that the peak rise in brain tumors and the introduction of aspartame occurred almost simultaneously, without the expected

period of latency, "it appears unlikely that any carcinogenic effect of aspartame ingestion could have accounted for the recent brain tumor trends as Olney et al. contend" (Gurney et al. 1997)

Aspartame Induces Lymphomas and Leukemias in Rats

In 2005 and 2006 Soffritti et al. of the European Ramazzini Foundation published a set of alarming study results. In fact, much of the concern regarding the safety of aspartame was generated by the initial findings of their research. In their study, the authors administered aspartame to male and female Sprague-Dawley rats with their feed. The rats, which were eight weeks old at the start of the experiment, were treated with aspartame containing feed until spontaneous death. The groups of 100-150/sex were given concentrations of 100,000; 50,000; 10,000; 2,000; 400; 80; and 0 ppm to simulate assumed daily intake by humans of 5,000; 2,500; 500; 100; 20; 4; and 0 mg/kg of body weight.

The study continued for 151 weeks until the death of the last rat at 159 weeks. Upon their deaths, the animals underwent complete necropsy and examination. The authors reported the following differences observed between the treated groups and the untreated control.

- 1. "An increase in malignant tumor-bearing animals with a significant positive trend in males...and in female...and a statistically significant difference in females treated at 50,000 ppm...,compared to controls;
- 2. An increased incidence of hyperplasia of the olfactory epithelium with a significant positive trend in males and females...;
- 3. An increase in the incidence of...carcinomas of the renal pelvis and ureter were observed in females...;
- 4. A dose-related increased incidence in malignant schwannomas of peripheral nerves was observed, with a significant positive trend in males..., while in females, nine malignancies were observed among treated animals of the different dosage groups and none among controls...;
- 5. A dose-related increased incidence in lymphomas-leukemias was observed, with a significant positive trend in males...and females. When compared to controls, a statistically significant difference was observed in females treated at doses of [400 ppm and above]..."

Finally, they also reported sparse brain malignancies observed in the treated groups, (among males and females,) whereas none were found in the control groups.

They concluded that, for the first time, they had demonstrated a dose-related, statistically significant increase in lymphomas and leukemias in females as a result of aspartame intake. Furthermore, they felt that these results were noted at levels close to those to which humans can be exposed. "Since the results of carcinogenicity bioassays in rodents, mainly rats and mice, have been shown to be a consistent predictor of human cancer risk," they closed their work by calling for an "urgent re-examination of permissible exposure levels of aspartame in both food and beverages" (Soffritti et al. 2006).

Evaluation of the European Ramazzini Foundation Study

Immediately following the publication of the disquieting carcinogenicity study carried out by the European Ramazzini Foundation, many scientists and researchers began to assess their reported results. As stated previously, the European Ramazzini Foundation "considered that the results of their study indicate that aspartame is a 'multipotential carcinogenic agent," leading to much concern. As a result, many specialists set out to attempt to either verify or discount their findings.

For example, after extensive evaluation, the European Food Safety Authority Panel concluded that the studies by the European Ramazzini Foundation contained "too many methodological flaws to be

taken into consideration when determining the carcinogenic potential of aspartame" and that the Panel had "no reason to revise the previously established acceptable daily intake for aspartame (European Food Safety Authority 2006). Below are a number of flaws which invalidate the findings of the European Ramazzini Foundation study.

Firstly, there was a high background incidence of chronic inflammatory disease among the colony of rats used (European Food Safety Authority 2006). This condition was not mentioned in the study. However, the fact that the colony was already suffering from chronic respiratory disease is a very plausible explanation of the lymphomas and leukemias that developed. This information, along with the lack of a positive dose-response relationship, makes it unlikely that the increased lymphomas and leukemias were related to aspartame.

Additionally, concerning the lesions of the renal pelvis, ureter, and bladder, although they were likely treatment related, the same results cannot be expected in humans due to differences between rat and human metabolism. Due to differences in urinary protein levels, rats are much more susceptible to these tumors than humans are when exposed to high doses of chemical irritants (Cohen 1995). According to the European Food Safety Authority panel, "It is widely accepted that the effect is a high dose effect of irritant chemicals or chemicals producing renal pelvic calcification as a result of imbalances in calcium metabolism, specific to the rat." The Panel did not consider these effects to be relevant to humans in any way.

Furthermore, the authors reported statistics for "total malignant tumors." However, aggregating all of the incidences of malignant tumors for statistical purposes was not justified given that the lymphomas, leukemias, and renal tumors should have been excluded, as explained above.

With regard to the malignant schwannomas, the number of tumors were low. Also, despite the fact that the dose-response relationship showed a positive trend in males, it was very flat over a wide range. The European Food Safety Authority panel felt that there was also general uncertainty as to the diagnoses of these tumors and that further histopathological peer-review of the relevant nervous system slides was necessary for complete evaluation.

Finally, actual human consumption of aspartame is far less than the concentrations at which the treated rats exhibited differences from the control group. Some might be tempted to say that carcinogenicity at high doses shows that there is carcinogenicity at low doses as well, but that it is at a lower rate, referred to as dose extrapolation. However, it is incorrect to automatically assume that this is so (Cohen 1995).

As a result of the numerous flaws present in multiple areas of the study findings, the results of the European Ramazzini Foundation study are considered invalid. Further studies were necessary to ascertain the safety of aspartame.

Consumption of Aspartame-Containing Beverages and Incidence of Hematopoietic and Brain Malignancies

In 2006, following multiple animal experiments which attempted to link aspartame to hematopoietic (pertaining to blood cell formation) and brain cancers, most importantly the seemingly positive linkage found in the European Ramazzini Foundation studies, a group of scientists set out to investigate the risks in humans. They "investigated the association between self-reported consumption of aspartame-containing beverages and incident hematopoietic and brain cancers."

The authors mailed out 3.5 million questionnaires to AARP members who were between the ages of fifty and seventy-one years old. Information about daily aspartame intake was obtained from these self-administered food frequency questionnaires. Of the 617,119 that were returned, 567,169 were satisfactorily completed. Excluded from the study were 52,887 persons with history of cancer, one

withdrawal, a number of duplicates, and people who had died. As a result, 473,984 questionnaires were considered, (285,079 men and 188,905 women).

During a follow up of more than five years, 1,888 hematopoietic cancers and 315 malignant gliomas (brain cancer) were discovered. These findings were largely comparable to overall rates of hematopoietic cancers and gliomas within the age range, for both the male and female subgroups. Moreover, the findings were not in any way linked to aspartame intake, nor was there any correlation between higher levels of aspartame intake and increased cancer risk.

As a result of their study, the authors concluded that their findings do not support the hypothesis that aspartame increases the risk of hematopoietic or brain cancer, and that it was in direct contradiction with the study conducted by the European Ramazzini Foundation. Furthermore, the authors noted the fact that the European Food Safety Authority dismissed the findings of the European Ramazzini Foundation due to the high background of chronic inflammatory conditions in the rat colony used, the lack of a dose-response, and other issues, as mentioned previously (Lim et al. 2006).

The study of Lim et al. has a number of strengths. First and foremost, the large sample size provided for more accurate results. Additionally, the fact that the dietary and lifestyle data was collected before the patients were diagnosed with cancer minimized the biases normally found due to differential reporting between cases and controls. (This is unlike the study by Gurney et al., for example, in which the data was collected from the mothers after their children had been diagnosed.) Furthermore, the food frequency questionnaire used was developed by the National Institute of Health in conjunction with the AARP through extensive cognitive testing.

(All the same, it is important to bear in mind that any information obtained through self-reporting by study members is bound to involve at least a small amount of bias.)

Conclusion

After thorough review of all of the scientific data available with regard to aspartame, there is no evidence that aspartame, as consumed by humans, is carcinogenic. Nevertheless, despite the lack of scientific evidence, many people feel that aspartame is "dangerous" and "causes cancer." Popular media often refers to aspartame with phrases like "deadly sweet" or "the sweet poison." Headlines like "Aspartame linked to cancer" are quickly believed and difficult to overturn in the minds of the public.

For example, following the European Ramazzini Foundation study in 2005, a branch of Harvard hospital promoted research which analyzed hospital records of tens of thousands of men and women. A report publicized by the hospital concluded that "those who drink a daily diet soda sweetened with aspartame could have an increased risk of leukemia, lymphoma, or non-Hodgkin's lymphoma." However, in actuality, the risk was prevalent among drinkers of mostly sugared soda, as well. The lead author of the study was asked whether the research proved that aspartame is dangerous, and she emphatically replied, "No, it does not" (Bazell 2012).

Subsequently, the hospital apologized and admitted that the science it promoted was weak. However, the damage was already done. In the words of Dr. Steven Nissen, chair of the Cleveland Clinic's cardiovascular medicine department, "Promoting a study that its own authors agree is not definite, not conclusive, and not useful for the public is not in the best interests of public health." Unfortunately, much of the commonly believed information about aspartame is exactly that, inconclusive data that was only intended to lead to further studying (Bazell 2012).

Despite the lack of evidence proving the carcinogenicity of aspartame, wouldn't it be better to stick to sucrose, which is considered "natural," and avoid the chemically produced aspartame? No. With the ever-growing obesity and obesity-related conditions, sucrose itself is like a toxin. Obesity related conditions are now the number one leading cause of preventable death in the United States. More than

one third of adults in the United States are obese, resulting in overwhelming numbers of conditions like heart disease, stroke, type 2 diabetes, and even obesity-related cancers (statistics based on review by the Centers for Disease Control and Prevention 2011).

Whereas the carcinogenic effects of aspartame in humans are doubtful, the deleterious effects of obesity are unambiguous and very alarming. So, where it's a question of the diet soda or a glass of water, no one would recommend the soda. However, when it's between a cup of juice and an aspartame-sweetened beverage, it is not so clear-cut. In essence it comes down to the question of which "poison" is worse.

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