

Aspartame: Is It Safe?

A Brief History

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Abstract

The food additive, L-aspartyl-1-phenylalanine-methyl-ester, or aspartame has been under scrutiny for the last 25 years since its introduction. The claims of its cancer causing ability especially an increased incidence of brain tumors and seizures are just some of the alleged side effects of this chemical's metabolism. From the start, the history of aspartame has been clouded by poor research by the manufacturer as well as poor judgement on the part of the FDA and their role in approving its use in over 4000 products today. The purpose of this article was to examine the research done over the last 30 years and to determine if aspartame is as safe as the NutraSweet® Company claims. Several side effects have been noted by people claiming to be sensitive to aspartame and its metabolic byproducts.

*It's a very odd thing
As odd as can be
That whatever Miss T eats
Turns into Miss T*

Walter de la Mare

Nothing is obvious to the uninformed.
Anonymous

Introduction

With the turn of the century and the new millenium just around the corner, the world has become an extremely fast paced and modern environment in which to live. This "giant leap for mankind" has brought with it both positive and negative aspects. Advances in communication, exploration, and education are but a few of the positive results. Pollution, hunger, and war are among the negative results. Pollution is one of the most counterproductive of all for not only do we pollute our planet, but we go as far as to pollute our bodies with chemicals and poisons of our modern world. Some of these are natural, and others are man-made. It is the man-made or synthetic compounds which are the biggest threat. The compounds that are discovered accidentally and then a use for them found are the worst of all. Such is the history of a compound known as L-aspartyl-

l-phenylalanine-methyl-ester or better known under the names of aspartame or NutraSweet®.

The researcher performed a systematic search of the literature spanning the last 30 years to discover the relevant information on the subject of aspartame and its possible link to problems such as an increase in brain tumors, seizures, and many others that have been reported.

Method

A search of original studies was done using a computerized Medline search engine which allowed the researcher to search articles from 1972 up to and including July 1997. Further articles and commentaries were gathered by the references of articles found in the original Medline search. Further government (FDA documentation) was gathered online through government offices online and other web sites dedicated to the release of public records.

Discussion

History

The aspartame story begins in 1964 when a group of scientists at G.D. Searle & Co. were given the task of looking for an inhibitor to the gastrointestinal tract hormone gastrin.¹ In December of 1965, James Schlatter, a scientist working on the team synthesized aspartyl-l-phenylalanine-methyl-ester. Mr. Schlatter was recrystallizing the compound from ethanol when some of the compound spilled on the outside of the flask. Later, he licked his finger to pick up a piece of paper and noticed the strong sweet taste. He believed that

the dipeptide was not toxic so he tasted a little and discovered its sweet taste. The discovery was reported in 1966 but no mention of the sweetness was made at that time.¹

G.D. Searle & Co. first reported the discovery in 1969 in the Journal of the American Chemical Society where researchers stated:

We wish to report another accidental discovery of an organic compound with a profound sucrose (table sugar) like taste...Preliminary tasting showed this compound to have a potency of 100-200 times sucrose depending on concentration and on what other flavors are present and to be devoid of unpleasant aftertaste.²

In 1970, the discovery was then published in the publication *Science*.³ That same year, G.D. Searle & Co. funded a study to evaluate the effects of aspartame in monkeys. Seven infant monkeys were fed aspartame with milk. One died after 300 days. Five of the remaining six had suffered from grand mal seizures on more than one occasion. The actual results were hidden from the FDA when G.D. Searle & Co. submitted their initial applications for aspartame's approval.⁴ Meanwhile, neuroscientist John W. Olney found that consumption of the amino acids glutamate, aspartate and cysteine caused brain damage in mice.^{5 6}

In 1973, Martha A. Freeman, M.D. of the FDA division of Metabolite and Endocrine Drug Products reported in a memorandum that "the information submitted for our review is inadequate to permit a scientific evaluation of clinical safety".⁷ This was based upon the material supplied by G.D. Searle & Co. Commenting on one particular single dose study she had this to say: "It is not feasible to extrapolate results of such single dose testing to the likely condition of use of aspartame as an artificial sweetener."⁹

It should be noted that the NutraSweet® Co. has used single dose studies as a basis for supporting the safety of aspartame and quelling the growing interest in the chemical safety.

The FDA approved aspartame for limited use on July 24, 1974. It was approved for use as "a free flowing sugar substitute, tablets for sweetening hot beverages, cereals, gum and dry bases."^{8 9} Before aspartame could go on the market, Dr. Olney, James Turner and LABEL Inc. (Legal Action for Buyer's Education & Labeling) filed a complaint with the FDA stating that they believed aspartame could cause brain damage. They were especially concerned about its affect on children.

As a direct result of Dr. Olney's persistence, the FDA started a special task force to look at the key studies for aspartame. Dr. Marvin Legator who was the primary toxicologist and the pioneer of mutagenicity testing at the FDA from 1969 to 1972 was asked by Common Cause Magazine to review the FDA investigation results of G.D. Searle & Co. tests. He had this to say:

[All tests were] scientifically irresponsible [and] disgraceful. I'm just shocked that that kind of sloppy [work] would even be sent to the FDA, and that the FDA administrators accepted it. There is no reason why these tests couldn't have been carried out correctly. It's not that we are talking about some great scientific breakthrough in methodology.¹⁰

The aspartame issue continued to be questioned from 1976 until 1981. G.D. Searle & Co. in the meantime was waging a legal battle as several of its products were under scrutiny because of poor research performed on the safety and side effects of these drugs. Those in question included the studies involved with the approval of Flagyl, Aldactone, Norpace and aspartame. Then on Jan. 21, 1981, the day after Ronald Reagan took office, G.D. Searle & Co. reapplied for approval of aspartame.¹¹ By July 1981

aspartame was approved for dry goods and was later approved for use in carbonated beverages (1983).

In house FDA scientists, as well as investigators, physicians, and various consumer groups protested the approval. Their complaints are part of the public record in the *Congressional Record Senate*. The FDA has subsequently denied any more requests for hearings regarding the safety of aspartame and its use in carbonated beverages. Since then, aspartame has been used in over 4000 products; they range from soft drinks to puddings, gelatins, cereals, gum, and over-the-counter medicines for treating childhood fever, headache and other infections.

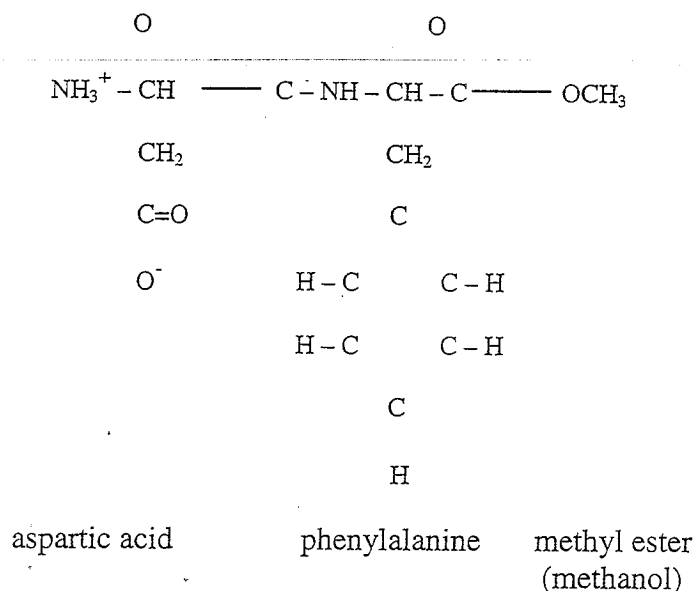
In 1985, Senator Howard Metzenbaum of Ohio introduced a bill called "Aspartame Safety Act of 1985" which would have required quantity labelling of aspartame on food items. It also mandated that there be a hold on new uses of aspartame until independent tests could be conducted by the National Institutes of Health. The bill was submitted to a Senate committee where it died shortly thereafter.

Meanwhile, G.D. Searle & Co. had a law suit brought against them by over 700 women who claimed that G.D. Searle's intrauterine device caused them pelvic inflammatory disease. G.D. Searle sold out to the chemical company, Monsanto. It was Monsanto that created the NutraSweet® Company as a separate subsidiary in 1985.

Chemical Makeup

In order to understand the possible dangers that aspartame holds, one must understand its chemical makeup and how it is metabolized by the human body. Aspartame has the chemical formula $C_{14}H_{18}N_2O_5$. The following is a diagram of the structure as arranged in aspartame:

Figure 1 Chemical Structure of L - aspartyl - 1- phenylalanine - methyl - ester.



Aspartame is composed of the following three components:

- I. phenylalanine ~ 50%
- II. aspartic acid ~ 40%
- III. methanol ~ 10%

Phenylalanine breaks down into a compound called diketopiperazine (DKP) when heated to 104 °F. When DKP is nitrosated by the gut, it produces a compound which closely resembles a powerful brain tumor causing agent called N-nitrosoare. ^{12 13} It is for this reason that the FDA mandated the warning label that states: PHENYLKETONURICS: Contains phenylalanine. Most forms of dietary protein which we consume contain 4 - 5% phenylalanine as opposed to over 50% in aspartame. Also, phenylalanine is one of the amino acid precursors to several neurotransmitters including dopamine, norepinephrine, and serotonin. ¹⁴ An excess of certain neurotransmitters is

known to over stimulate certain populations of nerve cells in the brain, even causing them to die.¹⁵

Aspartic acid or aspartate is considered an acidic amino acid and is very abundant in dietary protein. However, it is usually neutralized by the other basic and neutral amino acids when consumed in a natural form. Aspartate is very similar to glutamate which is an important neurotransmitter in the brain. The two of them have been coined excitotoxins because excessive amounts have been shown to cause nerve cell death.^{16 17 18} Glutamate has been scrutinized extensively because it is the primary ingredient in Monosodium Glutamate (MSG).

Finally, the methanol (wood alcohol) breaks down in solution (as in a diet soft drink) into formaldehyde. This happens more rapidly when the product is stored for an extensive length of time or it is heated. At 86 °F, 38% of aspartame decomposes and that increases to over 50% at 104 °F.¹⁶ The human liver normally breaks down the poisonous methanol into formaldehyde. The elimination of formaldehyde is a difficult process for the body so it attaches it to a water molecule to make it less toxic. It is then stored in areas of high lipid content. This includes the brain and nervous tissue. It is then converted to formate or formic acid (this is the active ingredient in ant poison powder) and finally CO₂ to be blown off by the lungs. The problem is that formate may contribute to metabolic acidosis and eye damage.^{19 20}

In conclusion, the NutraSweet® corporation has pointed out that a piece of fruit has more methanol than a can of diet soft drink (as advertised on the NutraSweet® web site). However, fruit contains the natural antidote for methanol which is ethanol. This minimizes the possible harm that the methanol could cause. In contrast, aspartame

contains no ethanol which is why the methanol in aspartame is unstable and can reduce to formaldehyde.

Consumption

The first year that records of aspartame consumption in the U.S. were made was 1984 in which 6.9 million pounds were consumed. That number jumped to 17.1 million pounds by 1987. That is an average of 7.0 pounds per capita or the equivalent of 16.1 billion pounds of sugar (based on aspartame being 150 times sweeter than sugar). The NutraSweet® Company stopped giving consumption records after 1987 to the Department of Agriculture.

Today, over 100 million Americans are consuming aspartame on a regular basis and this has produced over a billion dollars in sales for the NutraSweet® Company. Its influence is clearly visible that this product has a large economic impact as well. It continues to be used in more and more products. The international market for aspartame has begun to explode as aspartame was introduced to Europe (1988) and Asia (1992). Now that the patent on aspartame has expired, more and more companies are manufacturing aspartame so they can reap the benefits of this popular product.

Biological/Nutritional Impact

In 1985, the FDA started collecting information regarding adverse reactions to food ingredients. The following is a breakdown of complaints that the FDA received in 1996:

- 80 % Aspartame
- 15% Sulfites
- 5 % Other (includes MSG, food colorings and nitrites)

Of the over 10,000 complaints received, over 80 % concerned aspartame.²¹ The following table was compiled by HJ Roberts, M.D. and shows the major signs and symptoms of 551 so-called "aspartame reactors".

Table 1. Complaints in 551 aspartame reactors (Rounded Percentages).

Eye

Decreased vision and/or other eye problems (blurring, "bright flashes," tunnel vision)	140 (25%)
Pain (one or both eyes)	51 (9%)
Decreased tears, trouble with contact lens, or both	46 (8%)
Blindness (one or both eyes)	14 (3%)

Table 1. Complaints in 551 aspartame reactors -- continued.

Ear

Tinnitus ("ringing", "buzzing")	73 (13%)
Severe intolerance for noise	47 (9%)
Marked impairment of hearing	25 (5%)

Neurologic

Headaches	249 (45%)
Dizziness, unsteadiness, or both	217 (39%)
Confusion, memory loss, or both	157 (29%)
Severe drowsiness and sleepiness	93 (17%)
Parathesias ("pins and needles", "tingling") of numbness of the limbs	82 (15%)
Convulsions (grand mal epileptic attacks)	80 (15%)
Petit mal attacks and "absences"	18 (3%)
Severe slurring of speech	64 (12%)
Severe tremors	51 (9%)
Severe "hyperactivity" and "restless legs"	43 (8%)
Atypical facial pain	38 (7%)

Psychologic-Psychiatric

Severe depression	139 (25%)
"Extreme irritability"	125 (23%)
"Severe anxiety attacks"	105 (19%)
"Marked personality changes"	88 (16%)
Recent "severe insomnia"	76 (14%)
"Severe aggravation of phobias"	41 (7%)

Chest

Palpitations, tachycardia or both	88 (16%)
"Shortness of breath"	54 (10%)
Atypical chest pain	44 (8%)
Recent hypertension	34 (6%)

Gastrointestinal

Nausea	79 (14%)
Diarrhea (12 people had associated gross blood in stool)	70 (13%)
Abdominal pain	70 (13%)
Pain on swallowing	28 (5%)

Skin and Allergies

Severe itching without a rash	44 (8%)
Severe lip and mouth reactions	29 (5%)
Urticaria (hives)	25 (5%)
Other eruptions	48 (9%)
Aggravation of respiratory allergies	10 (2%)

Endocrine and Metabolic

Problems with diabetes: loss of control; precipitation of clinical diabetes; aggravation or simulation of diabetic complications	60 (11%)
Menstrual changes (22 females reported severe reduction of cessation of periods)	45 (8%)
Paradoxical weight gain	26 (5%)
Marked thinning or loss of hair	32 (6%)
Aggravated hypoglycemia	25 (5%)

Other

Frequency of voiding (day and night), dysuria, of both	69 (13%)
Excessive thirst	65 (12%)
Severe joint pains	58 (11%)
Bloating	57 (10%)
Fluid retention and leg swelling	20 (4%)
Increased susceptibility to infection	7 (1%)

The majority of aspartame reactors had multiple symptoms according to Dr. Robert's study.²²

Another aspect not covered by Dr. Robert's study was the potential link of aspartame to an increase in brain tumors. This was first proposed by Dr. Olney around the time aspartame was in the approval process. Dr. Olney used one of the first experiments done by G.D. Searle to point out the risk. He hypothesized that the by-product DKP was responsible for the increase in brain tumors. Although no studies have been done on humans and the possible link to brain tumors, it is interesting to note that from 1973 to 1990, brain tumors especially astrocytomas (the same ones found in the rat studies done by G.D. Searle in the late 1970's) increased 67% in the 65+ age category.²³

Also, in the same time period, brain tumors in all age groups jumped by greater than 10% with the greatest increase in incidence occurring in the years 1985-87.²³ Another particular type of rare brain tumor is the primary lymphoma of the brain. This is considered a very destructive tumor with a high mortality rate. There has been a dramatic increase in these previously rare tumors lately. Some scientist argue that the increase reflects advances made in diagnostic methods. But a recent study found this to be false and the author concludes that the increase is genuine.²⁴

Conclusion

The subject of aspartame's safety has been a hot topic for over 25 years now and with the continued concern over "the fattening of America" the public demand for more low-calorie products has increased the use of aspartame tremendously. As stated before, studies have shown (including the experiments performed by the manufacturer) that there is a link between many of the ailments that people are complaining about with regard to aspartame. Perhaps further use of this product should be halted until a definitive answer is provided to we, the consumer.

Recently, the FDA approved a new product for use as a sugar substitute called Sucralose®. It is made from natural sugar and has been chemically altered to allow it to pass through the gastrointestinal tract without being absorbed. The manufacturer states that unlike the fake fat, Olestra®, it does not cause intestinal discomfort. Also, because it is made from natural sucrose, it has the same sweet taste but no aftertaste that is associated with aspartame or saccharin. Sucralose® is supposedly 600 times sweeter than table sugar (aspartame is 150 times sweeter). Hopefully this product can be substituted for aspartame in many of the more heavily consumed products.

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