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Aspartame — a review

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Abstract

Aspartame (APM), a newly available synthetic sweetener approximately 180-200 times sweeter than sucrose, was approved for marketing by the FDA in 1981 following several years of scientific review. It is available in the United States for use as a sweetener in breakfast cereals, powdered beverages, gelatins, puddings, fillings, whipped toppings, chewing gum, soft drinks and as a table-top sweetener. Research to date has shown no harmful effects of APM consumption on the general population when consumed in amounts as much as two to three times the maximum expected daily ingestion levels. Aspartame is not indicated for use by individuals who have phenylketonuria. Dental research on APM has been limited thus far and its effect on dental health is yet to be established.

Aspartame (APM), a synthetic sweetener for food and beverages, was given final approval for marketing by the Food and Drug Administration (FDA) in 1981. A dipeptide based on two naturally occurring amino acids, aspartame is digested like a protein by the body and is 180-200 times as sweet as sucrose. The objectives of this paper are to review aspartame's approval by the FDA, to examine the dental research on aspartame, and to discuss the impact of this new sweetener on the dental health of the pediatric population.

Background

Aspartame was discovered accidentally in the late 1960s as a dipeptide having a pronounced sweet taste.[1] It is a synthetic combination of two amino acids, aspartic acid and phenylalanine. It is classified as a low-calorie, synthetic sweetener containing four kcal/gm. Because of its intense sweetness, only small amounts are required for sweetening. The amount of APM required to produce the sweetness equivalent to one teaspoon of sucrose produces only .1 kcal, compared to 16 kcal in one teaspoon of sugar. APM is marketed in the United States by G.D. Searle and Company under the names NutraSweet™ and Equal®. Equal, the powder, table-top form of APM, contains less than 1 gm of carbohydrate and provides 4 kcal per packet. According to reports from the manufacturer's taste tests, APM tastes more like sucrose than other sugar substitutes, and lacks the bitter after-taste of saccharin.

Aspartame may be used as a sugar replacement in a number of products such as breakfast cereals, topping mixes, frostings, confections, chewing gum, dry mix beverages, and yogurt. It also can be used in acidic foods such as fruit juices, soft drinks, and as a table-top sweetener (Figure 1). However, its uses are limited because APM becomes unstable at high temperatures and in alkaline environments. It cannot be used for baking or frying because it breaks down to form a substance known as diketopiperazine, which reduces sweetness.[2] APM-sweetened soft drinks have been available in Canada for the past two years but have not been available in the United States until recently. The delay was due primarily because of questions about APM's stability. When stored at less than ideal conditions, APM slowly loses sweetness in an acid solution, to the point where 50% of the initial sweetener has dissipated after six months. However, over the first 100 days this is a barely discernable difference in taste. As most soft drinks are consumed within 100 days of manufacture, the potential loss of sweetness is minimized[3-5] and this is no longer considered a deterent to placing the APM-sweetened beverages on the market. Also, by combining APM with the more stable sweetener, saccharin, the loss of sweetness due to APM's instability is minimized further.

The functional and property differences of APM do not make it suitable as a blanket substitute for sugar. However, it may be used in a variety of ways. APM can: (1) sweeten foods; (2) enhance flavors [particularly fruit flavors]; (3) reduce calories; (4) reduce volume and weight of presweetened products; (5) super-

Figure 1. More than 80 aspartame-sweetened products are available. These include soft drinks, dry beverage mixes, breakfast cereals, flavored gelatin and pudding mixes, whipped toppings, chewing gums, and a table-top sweetener.

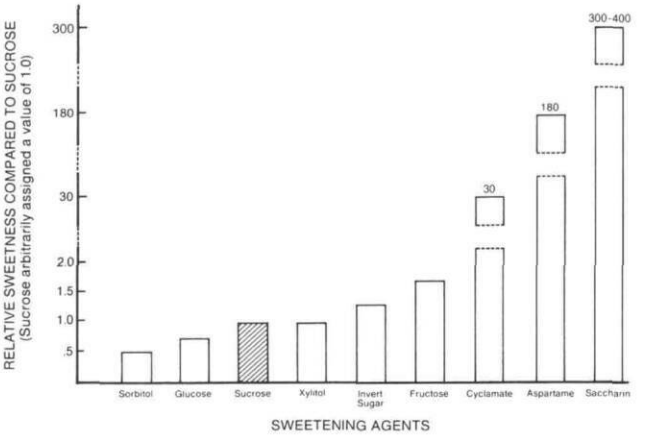

Figure 2. Relative sweetness of several sweeteners in comparison to sucrose.

sweeten products by adding concentrated sweetness as a small fraction of the total weight; (6) reduce viscosity, stickiness, or other properties associated with sugar; and (7) reduce sucrose consumption when indicated.[5]

Figure 2 illustrates the relative sweetness of APM and several other sweetening agents in comparison to sucrose. APM, saccharin, and cyclamates are intensely sweeter than sucrose.

Aspartame's FDA Approval

Approval of APM marketing to the public was a lengthy process involving several reviews before final approval. Beginning in 1973, four years following APM's discovery, Searle petitioned the FDA for approval to market APM as a sweetening agent in certain foods.

In July, 1974, the FDA granted approval for APM's use as petitioned, with three conditions regarding final product labeling. First, the label of any food containing APM was required to bear the following statement: "PHENYLKETONURICS: CONTAINS PHENYLALANINE." This was required to alert persons who must restrict their phenylalanine intake carefully (a discussion of the condition follows in a later section). The second condition was that when APM was to be used as a table-top sweetener, its label was required to bear instructions indicating that APM not be used in cooking or baking. The third condition stated that APM-containing foods which were being marketed for special dietary uses were required to be labeled in compliance with the FDA's special dietary foods regulation.[6]

Subsequent to approval, two parties formally objected to the approval on safety grounds, primarily the use of APM by children, asserting that the product might cause brain damage resulting in mental retardation, endocrine dysfunction, or both. Further hearings on APM's safety were ordered by the FDA and Searle agreed to delay the marketing of APM temporarily, pending resolution of the safety questions.

In December, 1975, the FDA ordered an immediate stay of APM's approval because the original safety studies conducted by Searle were brought into question. The original data from these studies was audited and reviewed by an independent third party, Universities Associated for Research and Education in Pathology (UAREP). In 1978, the UAREP report to the FDA concluded the Searle studies were valid.

Following this, a Board of Inquiry was appointed in 1979. The Board was composed of three scientists, agreed upon by Searle, the FDA, and the parties formally protesting APM's approval. The Board was charged with the responsibility to help resolve the following three issues and make appropriate recommendations to the commissioner of the FDA.

Issue 1: Whether the ingestion of APM, either alone or with glutamate, posed a risk of contributing to mental retardation, brain damage, or undesirable effects on neuroendocrine regulatory systems

Issue 2: Whether the ingestion of APM may induce brain neoplasms in rats

Issue 3: Based on findings of the above two issues, (a) should APM be allowed for use in foods? (b) if APM is allowed for use in foods, what labeling statements should be required?[7]

Upon review, the Board found that evidence did not indicate that APM would pose an increased risk to mental retardation. However, they did not rule out the possibility that APM might induce brain tumors in rats. For this reason, in October, 1980, the Board

recommended that APM not be approved for use in foods, pending further study.

In July, 1981, the commissioner of the FDA, Arthur Hayes, Jr., disagreed with the Board's concerns about brain tumors in rats and concluded that the available data established with reasonable certainty that APM did not cause brain tumors in laboratory rats. Therefore, he granted final approval to Searle to manufacture and market APM for use in foods. The conditions of labeling were the same as those required when APM was given its initial approval.[8] Following the commissioner's approval, two of the three members of the Board of Inquiry were convinced by the commissioner's rebuttal to their findings and approved release of the sweetener to the marketplace.[9] In a separate decision in July, 1983, approval was given for marketing APM in soft drinks in the United States.[10]

Saftey Issues

In light of the lengthy APM approval process, it is important to examine the issues of safety which were posed and which delayed its approval for a number of years. The main issues all have been stated previously, but they deserve further attention.

PKU

The risk associated with APM ingestion to the population of individuals who suffer from phenylketonuria (PKU) is well recognized[11] and undisputed. PKU is a genetic disorder that prevents phenylalanine metabolism and may lead to a progressive mental retardation if intake is not limited strictly. Individuals with PKU are almost always diagnosed shortly after birth and, when placed on restricted phenylalanine diets, do not develop brain damage. Because phenylalanine is one of the products of the hydrolysis of APM in the gut,[12] it should not be included in these individuals' diets, and hence, the FDA's labeling requirement for all foods containing APM.

Concerns have been raised regarding the safety of APM ingestion by individuals that are heterozygous for PKU, that is, an unaffected carrier of the PKU gene, and also for the fetus with undiagnosed PKU. However, these concerns appear to be unfounded. Two studies[13,14] involving PKU heterozygotes demonstrated no harmful effects to these individuals. The sweetener, when given in large doses, was well tolerated and showed no untoward medical or biochemical changes. In one of the studies,[14] patients who ingested 100 mg/kg daily (a very large dose) demonstrated plasma levels of phenylalanine which increased, but did not reach toxic levels.

Maternal Hyperphenylalanemia

There is evidence that harm may be done to the fetus of a woman with hyperphenylalanemia, which is a condition whereby a person's plasma phenylalanine levels are higher than normal, but lower than a person with PKU. The danger of a woman's developing hyperphenylalaninemia through ingestion of APM is highly improbable. According to FDA calculations, a 60 kg adult would need to consume 600 APM tablets or 24 liters of APM-sweetened beverage in a single sitting to reach the toxic threshold for fetal harm.[8] There are, however, several thousand women who reach childbearing age each year whose natural blood levels of phenylalanine fluctuate wildly, and in whom a smaller dose of APM could endanger the fetus. It is felt that these women are more vulnerable to the effects of phenylalanine that exists naturally in milk and meats and other high protein foods than to APM. Since it is impossible to keep the women from consuming these foods, it makes little sense to keep APM off the market for this reason.

Focal Brain Lesions/Neuroendocrine Changes

A second toxicity issue raised was whether the consumption of APM, either alone or with glutamate (i.e., as monosodium glutamate) poses a risk to humans of causing focal brain lesions and associated neuroendocrine changes which have been demonstrated in animals. Toxicity in this issue is related to concentrations of another metabolite of APM, aspartic acid.

Work by Olney and Ho[18] demonstrated damage to the hypothalamus when large doses of glutamate and aspartate were given to laboratory animals. The affected areas of the hypothalamus also are involved in endocrine control via the pituitary. Significantly, it is believed that the lesions could be produced by a single surge of glutamate and aspartate above some toxic threshold. These lesions have been demonstrated in neonatal mice administered high dosages of glutamate/aspartic acid by gavage,[18,19] but have not been found in primates.[19] The Board of Inquiry concluded that the amount of APM that would need to be ingested in a human diet in a single sitting to produce the lesions seen in rodents would be prohibitively high. The Board also concluded that there was not sufficient evidence that aspartic acid potentiated the effect of plasma glutamate to a significant degree.

Methanol

In addition to metabolites phenylalanine and aspartic acid, methanol also is formed by the degradation of APM. Few data on methanol toxicity are available. Toxicity from methanol appears to result from its metabolism to formaldehyde, which then is metabolized rapidly to formic acid, leading to the accumulation of formates. However, no formate is detected in the blood or urine after APM ingestion at levels as high as 200 mg/kg.[20]

Brain Tumors

The other major issue of concern was that APM may induce brain tumors in rats. The Bureau of Foods requires all food additives be assessed for carcinogenic potential in two rodent species, usually the mouse and the rat. Negative findings in both species is required for approval. Searle submitted the required studies and all parties agreed the mouse data to be negative; however, the data from three rat studies came under question. In one study the control group of rats had a higher incidence of tumors than the group exposed to APM, though not statistically significant. This result the Board termed bizarre and in its view justified dismissal of the study results. Searle, the FDA's Bureau of Foods, and ultimately the commissioner viewed the findings as a statistical anomaly and held the study to be valid.

Upon issuing his final approval, the commissioner stated that "few compounds have withstood such detailed testing and repeated, close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence concerning its safety."[8]

It is noteworthy that APM ingestion has shown no untoward effects when consumed by healthy children and adolescents,[15] by noninsulin-dependent diabetics,[16] and by young adults during weight reduction.[17]

Dental Research Involving Aspartame

The effects of APM on dental caries has been examined in only a limited manner to date. Most of the available data are based on in vitro experiments and have yielded conflicting results. Consequently, little is known about the effects of APM on dental health.

Breakdown of APM begins in the oral cavity as salivary enzymes begin to hydrolize it as protein.[21] In contrast to the metabolites of sucrose (glucose, fructose, and lactic acid), the metabolites of APM, (aspartic acid and phenylalanine) would not appear to contribute significantly to the decay process as cariogenic factors. Hence, one would expect the cariogenic potential of APM to be very low and thus a potentially strong preventive dentistry advancement when used as a sucrose replacement. Caustion must be expressed, however, before becoming overly excited about the prospects. It is unlikely that APM ever will replace sucrose completely because of APM's instability at high heat and over long periods of time. APM also lacks the bulk of sucrose which is desirable in some products. With this realization, most of the studies which have been completed have examined the effects of APM when present in addition to glucose or sucrose.

Linke and Chang[22] studied the effects of APM and a number of other sucrose substitutes on growth patterns and acid production of a glucose-grown *mutans* strain in vitro. They found that although APM alone could not sustain growth of the strains, when it was present in solution with glucose, it had little effect on the growth of *S. mutans*. Additionally, APM had no effect on the acid production of *S. mutans* during glucose fermentation. Somewhat different findings have been reported by others combining APM and sucrose.

Olson[23,24] examined the effects of APM when present in sucrose solution on adherent plaque formation of *S. mutans* in vitro. His findings, in part, were in agreement with Linke and Chang[22] in that he found no effect by APM on acid production and also that APM alone formed no adherent plaque. However, he found that APM combined with sucrose yielded a significant decrease in adherent plaque. It was felt that the decrease could be a result of one or more factors, including effects on the extracellular enzymes, on the ability of the bacteria to adhere, or on the ability of glucan to adhere.

Mishiro and Kaneko[25] also examined the acid production of plaque in glucose and APM mixtures. In contrast to the previously mentioned studies, they examined the response of plaque in human whole saliva. Their results were also in contrast to the others. They reported an increase in acid production of the mixture of APM and glucose, but, unexpectedly, an inhibited fall of pH of the plaque in the APM/glucose mixture. In other words, APM in combination with glucose seemed to be enhancing the lactic acid production of the plaque, yet inhibiting a fall in pH equal to the fall seen with glucose alone. These effects of APM could not be substituted by the constitutive amino acids, L-aspartic acid and L-phenylalanine, nor was there a difference in buffer capacity between APM and an amino acid solution.

Still other changes in pH have been reported with APM. Soparkar et al.[26] carried out an in vivo study examining the effects of different chewing gums on plaque pH. Utilizing a Kleinberg-type antimony electrode to measure plaque pH, they found that two commercially available sugarless gums, and a gum containing sorbitol, mannitol, and APM produced an increase in plaque pH, differing markedly from the depression of plaque pH produced by a chewing gum containing sucrose. In addition, when the APM gum was chewed for a 5-minute period 20 minutes following a sucrose rinse, the depressed pH rose rapidly above the initial level and then recovered to the initial level, while a sugar gum caused a relatively smaller rise and then a quick return to lower levels. APM alone as a sweetening agent was not evaluated so it is difficult to extrapolate any effects for which the APM may have been directly responsible. The authors do not offer explanations for the observed

changes in pH levels.

Only limited study has been reported thus far examining the effect of APM on dental caries. Reussner and Galimidi[27] carried out an investigation on laboratory rats inoculated with *S. mutans* and maintained on a modified basal cariogenic diet with either APM or saccharin added. APM demonstrated an insignificant dose-related decrease in buccal caries and insignificant decreases in occlusal dentinal caries. Saccharin showed a dose-related, significant decrease in occlusal dentinal caries. Similar findings have been reported by Tanzer and Slee.[28] In a later study, Reussner et al.[29] reported that APM reduced acid-induced enamel demineralization in laboratory rats. A saccharin solution of equivalent sweetness showed no such reduction.

Table I summarizes the dental research involving APM which, as stated previously, is limited to date and has given inconsistent findings. Both depression and elevation of plaque pH have been attributed to APM. When present in combination with glucose or sucrose APM has been shown to have no effect on acid production, but other investigations have shown it to produce increases in acid production. Clearly, further studies are indicated to examine more closely the effect of APM on the dental disease process.

Aspartame and the Pediatric Population

The impact of the sweetener APM on the population and specifically the dental health of the pediatric population is yet to be observed. It would seem that there could be some observable changes. A reduction of ingested sucrose is one such favorable response. The APM-sweetened products which are available currently and those proposed — such as breakfast cereals, dry mix beverages and soft drinks — are products which are consumed heavily in the pediatric age group. (A complete list of products currently marketed containing APM is available from the manufacturer.[a]) Substitution of the APM-sweetened products should decrease sucrose ingestion and potentially improve dental health. This, however, is yet to be shown, and any possible contributions to improved dental health would be merely speculative at this time. Certainly research in this area would be valuable.

Questions might be raised concerning the amounts of APM ingested by children, especially children with poorly supervised dietary habits who consume many soft drinks and other sweets daily. This was considered by the FDA before issuing final approval in 1981 and again with the approval of APM's use in soft drinks in 1983.[10] Estimated consumption levels were computed in several ways. Included were calculations based on: (1) substitution of APM for all sucrose in the diet and (2) substitution of APM for all dietary carbohydrate, both yielding levels obviously much higher than would ever be expected due to the fact that APM never will replace sucrose totally. Based on these calcuations, the intake value of 34 mg/kg/day was used in the assessment of possible toxicological risks. This figure represents the highest value obtained from any of the estimates of potential consumption. Levels two or four times the amount of this high estimate were used in investigations with human subjects with no ill effects observed.[15,16] Even higher dosages have been used in animal studies.[10] Based on projected maximum APM consumption levels, the commissioner of the FDA concluded that all available evidence established that these were "far, far below any level ever suspected of being toxic."[8] With the final approval in 1981, Searle agreed to monitor actual APM use levels to ensure that actual use remained well below suspected toxic levels. This monitoring is ongoing.

[a] Searle Food Resources, Inc.; Subsidiary of G.D. Searle and Co. Box 1111, Skokie, IL 60077.

Table 1. Relative Sweetness of Sweetening Agents Compared to Sucrose

SUMMARY OF FINDINGS OF DENTAL RESEARCH INVOLVING ASPARTAME
Effect on Growth of S. Mutans
APM alone does not sustain *S. mutans* growth
APM with glucose yields normal *S. mutans* growth
APM alone forms no adherent plaque
APM with sucrose yields a decrease in adherent plaque
Effect on Acid Production and Plaque pH
APM with glucose shows acid production equal to glucose alone
APM with glucose shows an increase in acid production but an inhibited fall in pH
APM with sucrose shows acid production equal to sucrose alone
APM with sorbitol and mannitol produces and maintains an increase in plaque pH which has been depressed with a sucrose rinse
Effect on Enamel Demineralization and Caries
APM reduces the amount of acid-induced enamel demineralization compared to a sucrose control
APM added to the diet of laboratory rats fed a basal cariogenic diet produces no significant changes in caries

Summary

Research at this time indicates that APM ingested within the suggested guidelines is safe for human consumption with no known harmful effects. The only exceptions are individuals with phenylketonuria who are advised against its ingestion.

No long-term human consumption studies are available at this time. Dental research on APM has

been slight and with mixed conclusions as to APM's effect on the dental disease process. Aspartame's impact on general dietary habits, reduction of sucrose intake, and dental health are yet to be documented.

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