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Aspartame: Scientific Evaluation in the Postmarketing Period

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Prior to marketing, the safety of the high-intensity sweetener aspartame for its intended uses as a sweetener and flavor enhancer was demonstrated by the results of over 100 scientific studies in animals and humans. In the postmarketing period, the safety of aspartame was further evaluated through extensive monitoring of intake, postmarketing surveillance of anecdotal reports of alleged health effects, and additional research to evaluate these anecdotal reports and other scientific issues. The results of the extensive intake evaluation in the United States, which was done over an 8-year period, and the results of studies done in other countries demonstrated intakes which were well below the acceptable daily intakes set by the FDA and regulatory bodies in other countries, as well as the Joint FAO/WHO Expert Committee on Food Additives. Evaluation of the anecdotal reports of adverse health effects, the first such system for a food additive, revealed that the reported effects were generally mild and also common in the general population and that there was no consistent or unique pattern of symptoms that could be causally linked to consumption of aspartame. Finally, the results of the extensive scientific research done to evaluate these allegations did not show a causal relationship between aspartame and adverse effects. Thus, the weight of scientific evidence confirms that, even in amounts many times what people typically consume, aspartame is safe for its intended uses as a sweetener and flavor enhancer.

***Key Words*: aspartame; postmarketing surveillance; intake; acceptable daily intake; ADI; anecdotal reports; safety; review.**

INTRODUCTION

Since regulatory approval 20 years ago, the high-intensity sweetener aspartame (L-aspartyl-L-phenylalanine methyl ester) has been consumed in more than 6000 products by hundreds of millions of people in countries around the world. Aspartame is unique among high-intensity sweeteners because it is metabolized by digestive esterases and peptidases to three common dietary components—the amino acids, aspartic acid and phenylalanine, and a small amount of methanol. These components are utilized by the body in the same way as when they are also derived from foods, such as meat, milk, fruits, and vegetables (Ranney *et al.*, 1976).

Further, the components of aspartame are derived in much larger amounts from these common foods. For example, a glass of milk provides about 6 times more phenylalanine and 13 times more aspartic acid and a glass of tomato juice provides about 6 times more methanol than an equivalent volume of beverage sweetened 100% with aspartame (Butchko and Kotsonis, 1989, 1991). Thus, much of the scientific research, both before and after regulatory approval, focused on the safety of these components.

Prior to marketing, aspartame underwent intensive scientific scrutiny and regulatory review. Extensive toxicologic and pharmacologic research was done in laboratory animals using much greater doses of aspartame than people would possibly ingest (Aspinall *et al.*, 1980; Bianchi *et al.*, 1980; Lennon *et al.*, 1980; Potts *et al.*, 1980; Saunders *et al.*, 1980; Molinary, 1984; Kotsonis and Hjelle, 1996). From the results of the toxicology studies, a no-observed-effect level (NOEL) of greater than 2000–4000 mg/kg body wt was established for aspartame. The animal toxicology data were used by the Scientific Committee for Food (1985) of the European Economic Communities, the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1980), and the Canadian HPB (Health and Welfare Canada, 1979) to establish an acceptable daily intake (ADI) of 40 mg/kg body wt for aspartame. When aspartame was first approved in the United States in 1974, the FDA authorized an ADI of 20 mg/kg body wt for aspartame (FDA, 1974). The ADI is the amount of an additive, which if consumed daily over a lifetime, would be considered safe and is usually 1% of the NOEL (Lu, 1988; Renwick, 1990, 1991).

Also prior to approval, the safety of aspartame and its metabolic constituents was assessed in humans in several subgroups: healthy infants, children, adolescents, and adults, obese individuals, diabetics, lactating women, and individuals heterozygous for the genetic disease phenylketonuria (PKU) who have a decreased ability to metabolize the essential amino acid phenylalanine. These and longer-term studies showed no

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untoward health consequences from aspartame (Hoffman, 1972, 1973; Langlois, 1972; Frey, 1973, 1976; Knopp *et al.*, 1976; Koch *et al.*, 1976; Stern *et al.*, 1976; Stegink *et al.*, 1977, 1979a,b, 1980, 1981a,b, 1983; Filer *et al.*, 1983). The results of the human studies, along with the animal research, provided convincing evidence that aspartame was safe for general use, including by pregnant women and children. The FDA responded to these additional data by increasing the ADI for aspartame to 50 mg/kg body wt in 1983 (FDA, 1984). The ADI for aspartame is the sweetness equivalent of a 60 kg person consuming approximately 600 grams (1.3 pounds) of sugar daily over a lifetime, an amount well above consumption patterns for sugar. In order to inform individuals with homozygous PKU, who cannot properly metabolize phenylalanine, the U.S. FDA and other regulatory agencies require a label statement on products with aspartame to indicate that the product contains phenylalanine.

Since approval, aspartame has undergone further investigation through postmarketing surveillance and research to evaluate various scientific issues. Research was done to evaluate aspartame intake levels relative to the ADI, as was extensive postmarketing surveillance of anecdotal reports of adverse health effects, the first such program for a food additive. In addition, several potential health issues, e.g., whether aspartame has an effect on headaches, allergies, seizures, behavior, cognitive function, etc., were evaluated through additional studies. The continued scientific evaluation of aspartame in the postmarketing period is discussed in this paper.

POSTMARKETING SURVEILLANCE: EVALUATION OF ASPARTAME INTAKE

As part of the safety evaluation for a food additive, regulators evaluate projected use levels relative to the ADI. If projected intake levels approach or exceed the ADI, restrictions may be imposed, such as limiting approvals for some categories of use to decrease potential exposure in the general population.

Before approval, projected average intake levels of aspartame in the United States ranged from 8.3 mg/kg/day, if all sucrose in an average-sized person's diet was replaced by aspartame, to 25 mg/kg/day if all dietary carbohydrate could be replaced by aspartame. Based on dietary records from about 12,000 individuals, it was estimated that, if all possible foods were replaced with aspartame-containing foods, the 99th percentile daily consumption of aspartame would be 34 mg/kg (FDA, 1981).

At the time of approval of aspartame, the FDA considered the 99th percentile estimated intake as representative of high-level consumers. Since that time, the FDA has determined that the 99th percentile is unduly conservative and probably unrealistic (FDA, 1986), as the very small number of consumers in the 99th percentile may have large and variable intakes, which may skew the data markedly. Thus, the FDA now uses projections at the 90th percentile as the benchmark of high-level consumers. The more conservative 97.5th percentile is used in the United Kingdom (MAFF, 1990).

Aspartame Intake in the United States

Actual aspartame consumption was tracked in the United States by MRCA Information Services (Northbrook, IL) (Abrams, 1986, 1992; Butchko and Kotsonis, 1991, 1994, 1996; Butchko *et al.*, 1994) from 1984 to 1992 through detailed menu census surveys from over 2000 households a year. During the 14-day survey, all foods eaten both at home and away from home were recorded.

Because of their smaller body weights, children may consume more of an additive on a milligram per kilogram basis than adults. To evaluate intake by children specifically, data also were recorded by age group: 0–23 months, 2–5 years, 6–12 years, 13–17 years, and 18 years and over, as well as all age groups together. In addition, intakes by special population subgroups such as diabetics and people on weight-reduction programs, who might be enthusiastic users of aspartame with potentially higher intakes, and women of childbearing potential and pregnant women were also monitored.

Because of its intense sweetness, only small amounts of aspartame are needed to sweeten foods (see Table 1). Thus, it would be expected that intake of aspartame would be low. The MRCA survey demonstrated that the average intake over the 14-day period for the general population of aspartame "eaters" (at the 90th percentile) ranged from 1.6 to 3.0 mg/kg/day. As shown in Table 2, intake of aspartame at the 90th percentile, even by children, diabetics, people on weight-reduction diets, and females of childbearing age, was only approximately 5–10% of the ADI in the United States.

Data from other types of consumption evaluations in the United States corroborate these results. Upon analysis of 1-day diary data from the U.S. Department of Agriculture (USDA) Continuing Survey of Food

TABLE 1
Approximate Aspartame Content of Some Common Foods

Food	Serving size	Aspartame content (mg)
Beverage	12 oz	180
Yogurt	8 oz	125
Gelatin dessert	4 oz	95
Hot chocolate	6 oz	50
Tabletop sweetener	1 packet	35
Pudding dessert	4 oz	25
Breath mint	1 mint	1.5

TABLE 2
Aspartame Intake (mg/kg/day) in the General Population and Various Subpopulations in the United States (90th Percentile, "Eaters" Only, 14-Day Average)

Survey dates	General population	2–5 years	Diabetics	Individuals on a reducing diet	Women of childbearing age
1984–1985	1.6	3.1	2.1	1.6	2.0
1985–1986	2.1	4.8	2.2	2.2	2.2
1986–1987	2.1	3.7	3.0	2.3	2.5
1987–1988	2.3	2.6	3.3	2.6	2.8
1988–1989	2.2	4.0	2.6	2.5	2.6
1989–1990	2.5	3.1	2.7	2.7	3.2
1990–1991	2.8	3.5	3.4	2.8	3.7
1991–1992	3.0	5.2	3.3	3.3	4.2

Intakes by Individuals (CSFII) from over 1500 women, aspartame intake ranged from 0 to 16.6 mg/kg/day; over 90% of the women who reported aspartame consumption had intakes less than 5 mg/kg/day (Heybach and Smith, 1988). Although per capita disappearance data may underestimate consumption since both eaters and "noneaters" are included, aspartame consumption for the total population (based on a 50-kg person) can be estimated to be about 1.6 mg/kg/day based on USDA per capita disappearance data (Heybach and Allen, 1988).

Aspartame Intake in Other Countries

The results of surveys from 10 other countries have found intake levels of aspartame to be remarkably consistent with those in the United States, and all are well below the ADI.

Australia. In 1994, mean consumption levels of aspartame were 6 and 7% of the ADI for all respondents to a 7-day survey and total consumers, respectively. The 90th percentile consumption was 23% of the ADI; however, the small sample made a precise estimate of 90th percentile intake difficult (National Food Authority, Australia, 1995).

Brazil. Median aspartame intake by the users of intense sweeteners was 2.9% of the ADI; median intakes by diabetics and individuals on weight-control regimens were 1.02 mg/kg/day (2.6% of the ADI) and 1.28 mg/kg/day (3.2% of the ADI), respectively (Toledo and Ioshi, 1995).

Canada. In 1987, the general population of aspartame eaters in Canada consumed 5.5 mg/kg/day during cold weather months and 5.9 mg/kg/day during warm weather months (7-day average, 90th percentile) (Heybach and Ross, 1989).

Finland. Nearly three-quarters (73%) of the diabetic children surveyed in Finland consumed aspartame-containing products, with a mean intake of 1.15 mg/kg/day, less than 3% of the ADI (Virtanen *et al.*, 1988).

France. From 1991 to 1992, aspartame intake was 0.6 and 1.0 mg/kg/day at the 90th and 95th percentiles, respectively (Chambolle *et al.*, 1994). A limitation of the study was that data for some categories were missing, and there were no data for food consumed outside the home. In a more recent study, intake of aspartame was evaluated in insulin-dependent diabetic children ages 2–20 years (Garnier-Sagne *et al.*, 1997) using a 5-day diary questionnaire. Intake by aspartame consumers at the mean, 97.5th percentile and maximum, were 2.4, 7.8, and 15.6 mg/kg/day, respectively. All sugar-free products were assumed to contain only one sweetener at its maximum authorized level; thus, estimations were very conservative.

Germany. In 1988–1989, consumption of the sweeteners aspartame, cyclamate, and saccharin was evaluated in Germany. The 90th percentile average daily intake for aspartame consumers was 2.75 mg/kg/day (Bar and Biermann, 1992).

Italy. Average aspartame intake among Italian teenagers who were known to be users of diet products was estimated to be only 0.03 mg/kg/day; the maximum aspartame intake was 0.39 mg/kg/day (Leclercq *et al.*, 1999).

Netherlands. Based on food frequency questionnaires, mean aspartame intake was estimated to be 2.4 mg/kg/day, with a 95th percentile intake of 7.5 mg/kg/day. Using food intake records, mean intake was 1.9 mg/kg/day while 95th percentile intake was 5.2 mg/kg/day (Hulshof and Bouman, 1995).

Norway. The average estimated intake of aspartame varied from 0.9 to 3.4 mg/kg/day among males and females and various age groups (Bergsten, 1993).

United Kingdom. In the United Kingdom in 1988, aspartame consumption (90th percentile) was 4% of the ADI or about 1.6 mg/kg/day. Children and diabetics ingested only 7 and 6%, respectively, of the ADI at the 90th percentile (Hinson and Nicol, 1992). From another

survey (MAFF, 1990), median and maximum aspartame intakes were 1.0 and 1.60 mg/kg/day, respectively, in 2- to 5-year-old children and 0.25 and 6.20 mg/kg/day, respectively, in 35- to 64-year-old adults. For the general population, median, maximum, and 97.5th percentile intakes were 16, 372, and 109 mg, respectively. For a 60-kg person, these are equal to 0.3, 6.2, and 1.8 mg/kg/day, respectively.

In 1994, the 97.5th percentile of aspartame consumption in diabetics was found to be 10.1 mg/kg/day, only about 25% of the ADI, even among individuals who would likely be frequent consumers of aspartame (MAFF, 1995).

Conclusion

Actual intake levels of aspartame were monitored from 1984 to 1992 through dietary surveys in the United States. Average daily aspartame intake at the 90th percentile (eaters only) in the general population ranged from about 2 to 3 mg/kg body wt. Consumption by 2- to 5-year-old children in these surveys ranged from about 2.5 to 5 mg/kg/day. Aspartame intake has also been estimated in several other countries. Although survey methodologies differed among these evaluations, aspartame intake is remarkably consistent across studies and is well below the ADI.

POSTMARKETING SURVEILLANCE: EVALUATION OF ANECDOTAL REPORTS OF HEALTH EFFECTS

In the 1940s and 1950s, when many new drugs were being developed and marketed, it was realized that the full spectrum of adverse reactions was not always apparent until a drug had been used by many patients over time (Faich, 1986). It was concluded that, along with extensive preapproval studies, a postmarketing surveillance system was needed to document and evaluate spontaneous reports of adverse reactions associated with marketed pharmaceuticals.

Shortly after aspartame's widespread marketing, there were a number of anecdotal reports of health effects, which some consumers related to their consumption of aspartame-containing products. Not unexpectedly, negative media stories influenced the numbers and types of these reports. The NutraSweet Company developed a postmarketing surveillance system for aspartame, based on the principles used for postmarketing surveillance of pharmaceuticals, to document and evaluate these anecdotal reports (Butchko and Kotsonis, 1994; Butchko *et al.*, 1994, 1996). Data from this system were evaluated by the company and also shared with the U.S. FDA, as discussed below.

Following the approval of aspartame in carbonated beverages in 1983, an increase in the reporting of adverse health events allegedly associated with the consumption of aspartame-containing products led the FDA to request the Centers for Disease Control (CDC) to evaluate these reports (Centers for Disease Control, 1984; Bradstock *et al.*, 1986). In 1985, the FDA's Center for Food Safety and Applied Nutrition (CFSAN) started its own process, the Adverse Reaction Monitoring System (ARMS), to monitor accounts of health problems anecdotally associated with consumption of foods, food and color additives, and vitamin/mineral supplements (Tollefson, 1988; Tollefson *et al.*, 1988).

Centers for Disease Control Evaluation

More than 500 reports were analyzed by the CDC, and almost half underwent detailed follow-up and evaluation. Most complainants were white women aged 21–60 years, randomly distributed throughout the United States with one exception. Aspartame had been subjected to substantial negative media coverage in Arizona, prompting proportionately more reports from that state. While reports were received about a variety of different symptoms, two-thirds fell into the neurologic/behavioral category. These consisted mostly of headache, mood alterations, insomnia, and dizziness. About a quarter of the reports were gastrointestinal, including abdominal pain, nausea, diarrhea, and vomiting (Centers for Disease Control, 1984; Bradstock *et al.*, 1986).

The CDC reported that "Despite great variety overall, the majority of frequently reported symptoms were mild and are symptoms that are common in the general populace" (Centers for Disease Control, 1984). No specific clinical syndromes that suggest a causal relationship with aspartame were observed. The CDC concluded that focused clinical studies would be the best way to address thoroughly the issues raised by the anecdotal reports (see Beyond Postmarketing Surveillance).

Food and Drug Administration ARMS

Unlike the case of pharmaceuticals, where most information is received from physicians, information regarding food additives is largely obtained from consumers. In the case of aspartame, about 70% of the reports in ARMS were provided by The NutraSweet Company. Reports to ARMS are categorized based on the severity of symptoms and on the basis of the consistency and frequency with which they occur. Any reports of a serious nature are investigated by FDA field inspectors through interviews and medical record review.

Based upon its review, the FDA concluded that there is no "reasonable evidence of possible public health harm" and "no consistent or unique patterns of symptoms reported with respect to aspartame that can be causally linked to its use" (Tollefson, 1988; Tollefson *et al.*, 1988).

In a 1995 FDA report on aspartame (FDA, 1995), a total of 7232 consumer reports had been received since marketing; only 11% were classified as serious.

Headache topped the list of symptoms reported, followed by dizziness, mood changes, and nausea/vomiting. The report noted the decline, since the peak in 1985, of reports from consumers regarding aspartame and further stated, "In summary, the number of adverse reaction complaints received by the FDA and the nature of these reports in terms of demographic distribution, severity, strength of association with the product, and symptoms remain comparable to those from previous analyses" (FDA, 1995).

FDA also separately analyzed the 251 reports of seizure anecdotally associated with aspartame consumption received through ARMS from 1986 to 1990 and concluded that almost half were highly unlikely to be related to aspartame (Tollefson and Barnard, 1992). Furthermore, the FDA could not exclude the possibility that the remaining reports had not simply occurred by chance. FDA concluded that the anecdotal reports "did not support the claim that the occurrences of the seizures were linked to consumption of aspartame" (Tollefson and Barnard, 1992). It was further concluded that the data did not suggest the need for a controlled clinical study to evaluate this issue.

The NutraSweet Company System for Health Report Evaluation

The NutraSweet Company's postmarketing surveillance system, which continued for 12 years after marketing in the United States, was a collaborative effort between the Consumer Center, where the staff was responsible for data collection, documentation, and follow-up, and the Clinical Research Group, where physicians provided medical expertise for evaluation of the reports. As noted in the CDC and FDA reports discussed above, symptoms allegedly associated with aspartame tended to be mild and were also common in the general population.

Not unexpectedly, the negative media stories and resulting controversy about aspartame in the early to mid-1980s had a significant impact on the number of anecdotal reports. As seen in Fig. 1, the number of reports increased markedly during that time and, as the controversy decreased in the late 1980s and early 1990s, the number of reports declined.

As there are more than 100 million aspartame users in the United States, it is inevitable that some of them will experience medical ailments temporally associated with consumption of an aspartame-containing product simply by chance. A temporal association does not mean a causal association. The error of associating causality to coincidence is perhaps best stated by one scientist who stated, "As aspartame is estimated to be consumed by about half the U.S. population, one need not be an epidemiologist to grasp the problem of establishing a cause-and-effect relationship. Half the headaches in America would be expected to occur in aspartame users, as would half the seizures and half the purchases of Chevrolets" (Raines, 1987).

Conclusion

The postmarketing surveillance of reports of adverse health effects allegedly associated with aspartame was the first such evaluation for a food additive. Extensive monitoring and evaluation of these reports over many years led to the conclusion that the reported symptoms generally were mild and common in the general population. There was no evidence to suggest a causal relationship with aspartame; however, "focused" clinical studies would be the best way to address thoroughly the issues raised by the anecdotal reports.

BEYOND POSTMARKETING SURVEILLANCE

Research to Evaluate Allegations of Health Effects

A number of studies, including focused clinical studies in humans, were done to address scientific issues, including the anecdotal reports of alleged health effects

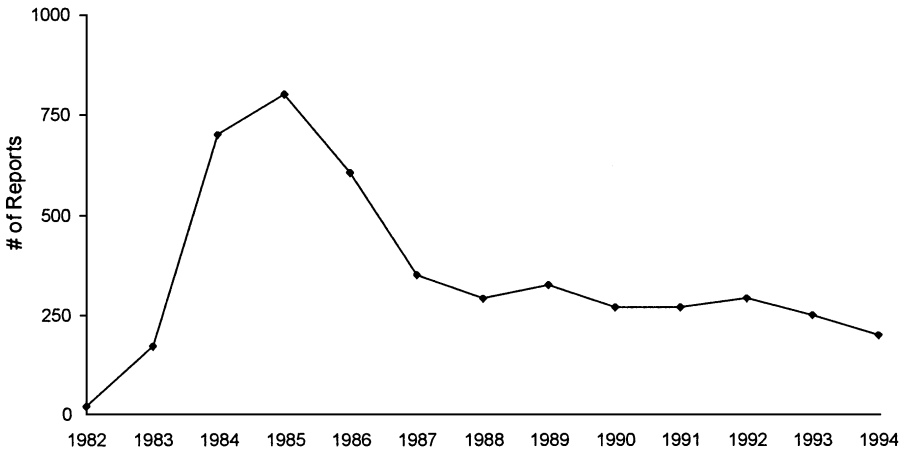

FIG. 1. Reports of health effects anecdotally associated with aspartame 1982–1994.

associated with aspartame. A long-term clinical study using high doses of aspartame (75 mg/kg/day for 24 weeks or about 25–30 times current consumption levels at the 90th percentile) resulted in no significant differences in clinical or biochemical parameters or adverse experiences compared with a placebo (Leon *et al.*, 1989). Focused clinical studies evaluated whether aspartame causes headache, seizures, or allergic-type reactions in individuals who firmly believed that aspartame caused their symptoms.

Headaches. Koehler and Glaros (1988) reported the results of an outpatient study to evaluate the effect of aspartame on the occurrence of migraine headache in migraineurs and concluded that aspartame caused a significant increase in the frequency of headaches but not in the intensity or duration of headaches. This study was criticized (Amery, 1988; Schiffman, 1988) because of several statistical issues that made it difficult to draw any valid conclusions from this study; data from only 11 of the 25 subjects were reported, and the effects on frequency of headaches can be attributed largely to data from only 2–3 subjects. From another outpatient study, Van Den Eeden *et al.* (1994) reported that subjects had more days with headaches, but there was no difference in the length or intensity of headaches. This study was criticized (Levy *et al.*, 1995; Schiffman, 1995) because the results from one subject of the 32 enrolled largely accounted for any difference between aspartame and placebo. When individuals who were convinced that aspartame had caused their headaches were evaluated in a randomized, double-blind, placebo-controlled study in the controlled environment of a Clinical Research Unit at Duke University, aspartame (at a dose about 10 times 90th percentile consumption) was no more likely than a placebo to elicit headache (Schiffman *et al.*, 1987).

Allergenicity. Early on, Kulczycki (1986) reported a single case report of an individual he believed was allergic to aspartame. Geha and co-workers (1993) later reported the results of a multicenter, randomized, double-blind, placebo-controlled, crossover study done with individuals who were convinced they were allergic to aspartame. These investigators concluded that aspartame and its conversion products are no more likely than a placebo to cause allergic-type reactions. Another study also demonstrated that alleged allergic-type reactions to aspartame were not reproducible under blinded conditions (Garriga *et al.*, 1991).

Brain function: Neurotransmission, cognition, behavior, mood, and seizures. A number of the aspartame allegations centered on various aspects of brain function. The underlying hypothesis was that aspartame, as a source of phenylalanine without the other large neutral amino acids (i.e., tryptophan, valine, leucine, isoleucine, methionine, histidine) which compete for transport across the blood–brain barrier, would increase the serum ratio of phenylalanine to the other large amino acids (Phe/LNAA), thereby selectively increasing brain phenylalanine concentrations. It was further hypothesized that such increased entry of phenylalanine into the brain may result in disturbances in monoaminergic neurotransmission (Wurtman, 1983).

However, review of the numerous studies in laboratory animals evaluating whether aspartame has an effect on various brain neurotransmitter systems has shown no consistent effects of enormous amounts of aspartame (Schomer *et al.*, 1996). In addition, the results of additional animal studies demonstrated that increases in brain phenylalanine concentrations after enormous doses of aspartame do not affect brain monoaminergic neurotransmission (Garattini *et al.*, 1988; Perego *et al.*, 1988; Reilly *et al.*, 1989, 1990). Furthermore, any effect that aspartame may have on the selective entry of phenylalanine into the brain is not unique to aspartame. For example, consumption of equisweet amounts of sugar has similar effects on the Phe/LNAA, through insulin-mediated changes in the serum concentrations of these amino acids (Martin-Du Pan *et al.*, 1982; Stegink *et al.*, 1987; Wolf-Novak *et al.*, 1990; Burns *et al.*, 1991).

Furthermore, numerous studies in humans have demonstrated that even massive doses of aspartame, many times those typically consumed, have no effect on cognitive performance, mood, or behavior compared to a placebo (Wolraich *et al.*, 1985, 1994; Ferguson *et al.*, 1986; Goldman *et al.*, 1986; Milich and Pelham, 1986; Kruesi *et al.*, 1987; Ryan-Harshman *et al.*, 1987; Lieberman *et al.*, 1988; Dodge *et al.*, 1990; Lapierre *et al.*, 1990; Saravis *et al.*, 1990; Stokes *et al.*, 1991, 1994; Shaywitz *et al.*, 1994a; Trefz *et al.*, 1994; Spiers *et al.*, 1998). These studies were done in both healthy children and adults, including college students and pilots, as well as in subpopulations who were thought to be possibly "more sensitive," such as children with attention deficit disorder and adults who are heterozygous for phenylketonuria (PKUH). Various assessments of mood, behavior, and cognitive performance were utilized in these studies. For example, in the study in PKUH, a computerized battery of tests that had been shown to detect subtle changes in cognitive performance not detected by conventional tests, and computerized, spectral analysis of the electroencephalograms were used (Trefz *et al.*, 1994).

From a study in depressed patients, Walton *et al.* (1993) concluded that aspartame increased the frequency and severity of adverse experiences in these individuals. The study was designed to include 40 depressed subjects and 40 nondepressed subjects. However, only 13 subjects (8 with depression and 5 without depression) were enrolled before the study was stopped, and only 11 completed the study. This study has been criticized (Butchko, 1994; Schomer *et al.*, 1996) because the authors apparently combined unrelated adverse

complaints to show a statistically significant result, as there were no differences between aspartame and placebo in specific types of complaints.

Numerous studies were done in various animal models of epilepsy ranging from studies in both epileptic and nonepileptic rats, mice, and epileptic baboons. Enormous doses of aspartame or phenylalanine (in the range of thousands of mg/kg body wt) were used in these studies. From the results, there is compelling evidence that aspartame is not a proconvulsant (Guiso *et al.*, 1988, 1991; Pinto and Maher, 1988; Cain *et al.*, 1989; Dailey *et al.*, 1989, 1991; Fisher, 1989; Meldrum *et al.*, 1989; Sze, 1989; Tilson *et al.*, 1989; Zhi and Levy, 1989; Diomede *et al.*, 1991; Jobe *et al.*, 1992; Jobe and Dailey, 1993; Lajtha *et al.*, 1994; Sperber *et al.*, 1995; Helali *et al.*, 1996).

From a study in children with absence seizures, Camfield and co-workers (1992) reported that aspartame compared to sugar may increase the amount of EEG spike-wave activity. However, according to Shaywitz and Novotny (1993), sugar is not a true "placebo" as it may affect the EEG and thus may have confounded the results. Further, the baseline period of the study was too short to have been able to determine reliably if aspartame had an effect. Rowan *et al.* (1995) reported the results of a randomized, double-blind, placebo-controlled, crossover study with 5 continuous days of EEG monitoring in a clinical research unit with individuals who were convinced that aspartame caused their seizures. With doses of aspartame about 17 times 90th percentile consumption, there was no evidence of aspartame-activated epileptiform activity, and aspartame was no more likely than placebo to cause seizures. Shaywitz *et al.* (1994b) reported the results of a 4-week study in children with seizure disorders, including absence seizures. After a dose about 10 times 90th percentile intake levels, aspartame neither provoked nor exacerbated seizures nor altered EEG activity compared to placebo.

That aspartame does not affect brain function is not surprising considering that consumption of aspartame-sweetened foods does not increase plasma phenylalanine concentrations beyond those which normally occur postprandially (Stegink *et al.*, 1977, 1979a, 1980). For example, doses of aspartame of approximately 30 mg/kg/day (about 10 times 90th percentile daily intake) do not increase plasma phenylalanine concentrations above those observed after eating a protein-containing meal in normal adults, phenylketonuric heterozygotes, or non-insulin-dependent diabetic populations (Filer and Stegink, 1989).

Further, at current levels of consumption, only a small fraction of daily dietary intake of aspartic acid and the essential amino acid phenylalanine by adults and children is derived from aspartame (Butchko and Kotsonis, 1989, 1991, 1996) (Figs. 2 and 3). The only individuals who must be concerned regarding aspartame's phenylalanine content are those with phenylketonuria, a rare genetic disease in which the body cannot properly metabolize phenylalanine. These individuals must severely restrict phenylalanine intake from all dietary sources, including aspartame.

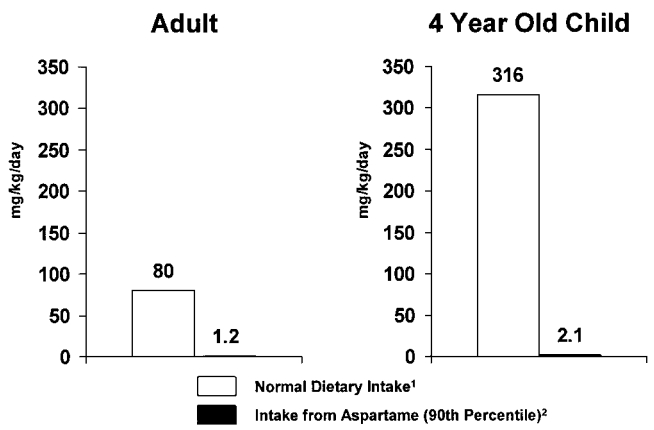

FIG. 2. Intake of aspartic acid from the normal diet compared to that from aspartame (90th percentile, 14-day average, "eaters" only) in adults and 4-year-old children.

Methanol. Aspartame yields approximately 10% methanol by weight. The amount of methanol released from aspartame is well below normal dietary exposure to methanol from fruits, vegetables, and juices (Butchko and Kotsonis, 1989, 1991). Aspartame, even in amounts many times those consumed from products, does not significantly change baseline blood concentrations of methanol or formate (Stegink *et al.*, 1981a, 1983). Whereas methanol exposure at the 90th percentile of chronic aspartame consumption is 0.3 mg/kg/day, the FDA has established acceptable levels of exposure to methanol at 7.1 to 8.4 mg/kg/day for 60 kg

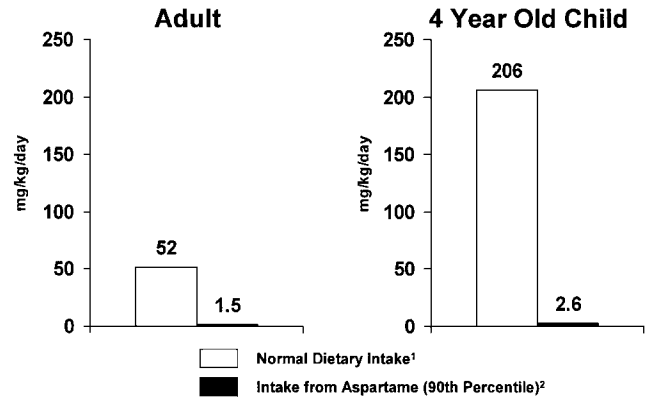

FIG. 3. Intake of phenylalanine from the normal diet compared to that from aspartame (90th percentile, 14-day average, "eaters" only) in adults and 4-year-old children.

adults (FDA, 1996b). Thus, acceptable dietary exposure to methanol is approximately 25 times potential exposure to methanol following 90th percentile consumption of aspartame.

Recently, Trocho *et al.* (1998) concluded from a study in rats that aspartame may be hazardous because formaldehyde adducts in tissue proteins and nucleic acids from aspartame may accumulate. However, according to Tephly (1999), the doses of aspartame used in the study do not even yield blood methanol concentrations outside control values. Further, the amount of aspartame equal to that in about 75 servings (12 oz) of beverage as a single bolus for an adult human results in no detectable increase in blood formate concentrations in humans, whereas increased urinary formate excretion shows that the body is well able to handle even excessive amounts of aspartame. In addition, there is no accumulation of blood or urinary methanol or formate with long-term exposure to aspartame. Thus, Tephly (1999) concluded, "the normal flux of one-carbon moieties whether derived from pectin, aspartame, or fruit juices is a physiologic phenomenon and not a toxic event."

Brain tumors. Olney *et al.* (1996) claimed that the reported increased rate of brain tumors in the United States may be associated with the marketing of aspartame. However, according to Levy and Hedeker (1996), the arguments of Olney *et al.* implicitly require two biologically indefensible assumptions: first, that a certain factor (aspartame) could cause an observed increase in the incidence of brain cancer in less than 4 years and second, that even more widespread exposure to this factor would cause no further increase in the incidence of that cancer in subsequent years. The fact is that the trend of increased brain tumor rates started well before aspartame was marketed, and overall brain tumor rates have actually been decreasing since about 1990 (Levy and Hedeker, 1996; National Cancer Institute, 1999) (Fig. 4).

Further, the pattern of increased brain tumor rates has been noted primarily in the very elderly (Greig *et al.*, 1990; Davis *et al.*, 1991; Muir *et al.*, 1994; Werner *et al.*, 1995), not the typical age group of aspartame consumers. In addition, it is widely thought that apparent increases in brain tumor rates in the mid-1980s may not reflect genuine increases in brain tumors but rather enhanced detection, largely resulting from the availability of sophisticated noninvasive diagnostic technology, such as CT and MRI (Boyle *et al.*, 1990; Greig *et al.*, 1990; Marshall, 1990; Davis *et al.*, 1991; La Vecchia *et al.*, 1992; Modan *et al.*, 1992; Muir *et al.*, 1994; Werner *et al.*, 1995; Legler *et al.*, 1999).

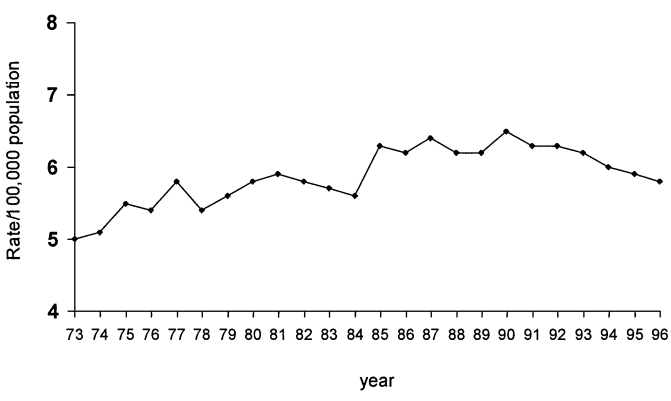

FIG. 4. Yearly age-adjusted brain tumor rates from the National Cancer Institute SEER registry (1973–1996).

Epidemiologists have criticized Olney and coworkers' attempted association between the introduction of aspartame and occurrence of brain tumors (Davies *et al.*, 1996; Ross, 1998). For example, Ross stated, "From an epidemiologic perspective, the conclusion of this report may well represent a classic example of 'ecologic fallacy' ... There is no information available regarding whether the individuals who developed brain tumors consumed aspartame. For example, one might also invoke (a) cellular phone, home computer, and VCR usage; (b) depletion of the ozone layer; or (c) increased use of stereo headphones as potentially causative agents ... some or all of these possibilities may or may not have any biological plausibility to the observed associations."

In addition, a case-control study, which specifically evaluated aspartame consumption and the risk of childhood brain tumors, was published by Gurney *et al.* (1997). In this study, case patients were 19 years of age or older and were diagnosed with a primary brain tumor between 1984 and 1991. The results of the study showed that children with brain tumors were no more likely to have consumed aspartame than control children, nor was there any elevated risk from maternal consumption of aspartame during pregnancy.

Olney's involvement with this issue began before aspartame approval in the United States when he claimed to the FDA and the Public Board of Inquiry (PBOI), appointed by FDA to review his concerns (FDA, 1981), that the results of studies in rats indicated that aspartame may cause brain tumors. At that time, he claimed that aspartame-fed rats had a higher rate of brain tumors than control rats in one study and that another lifetime rat study, including *in utero* exposure to aspartame, was unreliable because the brain tumor incidence was too high in the control group. The underlying basis for such claims is the incorrect assertion that the background incidence of brain tumors in Sprague–Dawley (SD) rats is 0.1%; the actual background incidence is at least 20–30 times higher (Koestner, 1984, 1997).

FDA (1981) concluded that there was no dose-dependent increase in brain tumors or any expected characteristic of carcinogens in the rat carcinogenicity studies. An additional study done in mice further demonstrated that aspartame was not carcinogenic

(FDA, 1981), and a subsequent third, 2-year rat study also confirmed that aspartame was not carcinogenic (Ishii, 1981, 1984). Thus, the results of three rat and one mouse studies evaluating the carcinogenicity of aspartame demonstrate that aspartame is not a carcinogen, even at dosages hundreds of times higher than the 90th percentile of human consumption (FDA, 1981; Ishii, 1981, 1984; Cornell *et al.*, 1984; Koestner, 1984, 1997; Flamm, 1997).

Although the PBOI appointed by FDA to review Olney's concerns of neurotoxicity and brain tumors initially could not reach a decision regarding aspartame and brain tumors (FDA, 1980), the additional considerations and findings in animals summarized above prompted a letter (Nauta, 1981) dated August 6, 1981, to FDA Commissioner Hayes from Dr. Nauta, Chairman of the PBOI, who stated in regard to aspartame's approval by FDA: "... had we known earlier about the reassuring outcome of the recent Japanese oncogenicity studies, our recommendation would doubtless have been for unqualified approval ... we wish to express our endorsement of your final decision in this matter."

The allegations by Olney and co-workers regarding aspartame and brain tumors have been evaluated by scientists at government and regulatory agencies in the United States, the United Kingdom, the European Union, Australia, and Brazil:

—The U.S. National Cancer Institute (NCI) (1997) concluded, "a recent analysis of the NCI statistics on cancer incidence in the United States does not support an association between the use of aspartame and an increased incidence of brain tumors."

—The U.S. FDA concluded that the analysis "does not support an association between the use of aspartame and increased incidence of brain tumors" (FDA, 1996a).

—In the UK, the Committee on Carcinogenicity at the Department of Health stated, "The Committee concluded that the data published by Olney *et al.* did not raise any concerns with regard to the use of aspartame in the United Kingdom" (Department of Health, 1998; MAFF, 1999).

—The Scientific Committee for Food (1997) of the European Union concluded, "... the data do not support the proposed biphasic increase in the incidence of brain tumors in the USA during the 1980's."

—The Australia/New Zealand Food Authority (ANZFA, 1997) concluded, "From the extensive scientific data available at this stage, the evidence does not support that aspartame is carcinogenic in either animals or humans. There appears to be no foundation to recent USA reports of increased brain tumors in humans."

—Finally, after an expert analysis, the Brazilian Ministry of Health concluded that aspartame does not cause brain tumors (Agencia Saude, 1999).

Conclusion

Allegations regarding aspartame and adverse health effects in the postmarketing period were evaluated through additional scientific studies in both laboratory animals and humans. The results of these studies confirmed the results of the previous studies demonstrating that aspartame is safe and not associated with adverse health effects.

CONCLUSIONS

In accordance with regulatory requirements, prior to marketing, aspartame was demonstrated to be a safe sweetener for its intended uses based on the results of over 100 scientific studies in animals and humans. In the postmarketing period, the safety of aspartame was further confirmed through extensive monitoring of intake vs the ADI, postmarketing surveillance of anecdotal reports of adverse health effects, and postmarketing research to evaluate these allegations and other scientific issues in controlled, scientific studies.

The results of the intake studies, despite differences in methodology, demonstrated consistent intakes in various countries that were well below the ADI; analysis of the postmarketing surveillance of consumer reports of adverse health effects revealed no consistent pattern of symptoms that could be causally related to consumption of aspartame; and the results of scientific studies to evaluate these allegations did not show a causal relationship between aspartame and alleged adverse effects. Thus, the totality of scientific evidence clearly demonstrates that, even in amounts many times what people typically consume, aspartame is safe (Stegink and Filer, 1984; American Medical Association, 1985; Stegink, 1987a,b; Janssen and van der Heijden, 1988; Butchko and Kotsonis, 1989; Fisher, 1989; Sze, 1989; Fernstrom, 1991; Jobe and Dailey, 1993; Lajtha *et al.*, 1994; Tschanz *et al.*, 1996).

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