The Aspartame Controversy

While questions about saccharin may persist, the safety of another artificial sweetener, aspartame, is clear cut, say FDA officials. FDA calls aspartame, sold under trade names such as NutraSweet and Equal, one of the most thoroughly tested and studied food additives the agency has ever approved. The agency says the more than 100 toxicological and clinical studies it has reviewed confirm that aspartame is safe for the general population.

This message would not necessarily be apparent to consumers surfing the Internet, especially those who use Web-based search engines to find information about sugar substitutes or artificial sweeteners. Websites with screaming headlines and well-written text attempt to link aspartame consumption to systemic lupus, multiple sclerosis, vision problems, headaches, fatigue, and even Alzheimer's disease. One report distributed nationally over e-mail systems claims that aspartame-sweetened soft drinks delivered to military personnel during the Persian Gulf War may have prompted Gulf War syndrome.

No way, says FDA, along with many other health organizations such as the American Medical Association. David Hattan, Ph.D., acting director of FDA's division of health effects evaluation, says there is no "credible evidence," to support, for example, a link between aspartame and multiple sclerosis or systemic lupus. Some Internet reports claim that patients suffering from both conditions went into remission after discontinuing aspartame use. "Both of these disorders are subject to spontaneous remissions and exacerbation," says Hattan. "So it is entirely possible that when patients stopped using aspartame they might also coincidentally have had remission of their symptoms."

It is true, says Hattan, that aspartame ingestion results in the production of methanol, formaldehyde and formate--substances that could be considered toxic at high doses. But the levels formed are modest, and substances such as methanol are found in higher amounts in common food products such as citrus juices and tomatoes.

Other circulating reports claim that two amino acids in aspartame--phenylalanine and aspartic acid--can cause neurotoxic effects such as brain damage. "This is true in certain individuals and in high enough doses," says Hattan. He explains that a very small group of people who have the rare hereditary disease phenylketonuria, estimated at 1 in 16,000 people, are sensitive to phenylalanine. These "phenylketonurics" have to watch their intake of phenylalanine from other sources as well. People with advanced liver disease and pregnant women with high levels of phenylalanine in the blood also may have trouble metabolizing the substance. FDA requires all products containing aspartame to be labeled for phenylalanine so consumers will be aware of the substance's presence and can avoid or restrict it.

Aspartic acid also has the potential to cause brain damage at very high doses. But under normal intake levels, the brain's mechanism for controlling aspartic acid levels ensures no adverse effects. It is unlikely that any consumer would eat or drink enough aspartame to cause brain damage: FDA figures show that most aspartame users only consume about 4 to 7 percent of the acceptable daily intake the agency has set for the sweetener.

Still other reports attempt to link aspartame to seizures and birth defects. Regarding seizures, Hattan cites animal and human studies showing that the sweetener neither causes nor enhances the susceptibility of seizures. Aspartame also has been evaluated for its potential to cause reproductive effects or birth defects. Again, researchers found no evidence, even in test animals fed the sweetener at doses much higher than those to which humans would be exposed.

Approved in 1981, aspartame is 180 times sweeter than sugar. It is used in products such as beverages, breakfast cereals, desserts, and chewing gum, and also as a tabletop sweetener. In 1996, a study raised the issue that aspartame consumption may be related to an increase in brain tumors following FDA's approval of the sweetener in 1981. But analysis of the National Cancer Institute's database on cancer incidence showed that cases of brain cancers began increasing in 1973--well before aspartame was approved--and continued to increase through 1985. In recent years, brain tumor frequency has actually decreased slightly. NCI currently is studying aspartame and other dietary factors as part of a larger study of adult brain cancer.

Aspartame and the Internet

The following letter appeared in The Lancet on 3 July 1999. It is reproduced here with the permission of the publishers of this respected journal.

Sir - Patients at our diabetes clinic have raised concerns about information on the internet about a link between the artificial sweetener aspartame and various diseases. Our research revealed over 6000 web sites that mention aspartame, with many hundreds alleging aspartame to be the cause of multiple sclerosis, lupus erythematosis, Gulf War Syndrome, chronic fatigue syndrome, brain tumours, and diabetes mellitus, among many others. Virtually all of the information offered is anecdotal, from anonymous sources and is scientifically implausible.

Aspartame, a dipeptide composed of phenylalanine and aspartic acid linked by a methyl ester bond, is not absorbed, and is completely hydrolysed in the intestine to yield the two constituent amino acids and free methanol. Opponents of aspartame suggest that the phenylalanine and methanol so released are dangerous. In particular, they assert that methanol can be converted to formaldehyde and then to formic acid, and thus cause metabolic acidosis and neurotoxicity.

Although a 330 ml can of aspartame-sweetened soft drink will yield about 20 mg methanol, an equivalent volume of fruit juice produces 40 mg methanol, and an alcoholic beverage about 60-100 mg. The yield of phenylalanine is about 100 mg for a can of diet soft drink, compared with 300 mg for an egg, 500 mg for a glass of milk, and 900 mg for a large hamburger (1). Thus, the amount of phenylalanine or methanol ingested from consumption of aspartame is trivial, compared with other dietary sources. Clinical studies have shown no evidence of toxic effects and no increase in plasma concentrations of methanol, formic acid, or phenylalanine with daily consumption of 50 mg/kg aspartame (equivalent to 17 cans of diet soft drink daily for a 70 kg adult) (1, 2).

The anti aspartame campaign purports to offer an explanation for illnesses that are prominent in the public eye. By targeting a manufactured chemical agent, and combining this with pseudo-science and selective reporting, the campaign makes complex issues deceptively simple. Sensational web site names (eg, aspartamekills.com) grab the browser's attention and this misinformation is also widely disseminated via chat groups and chain e-mail.

People consult the internet about medical issues for various reasons and many users regard online sources as being authoritative and valid. The medical profession has a role in teaching our patients to be discriminating consumers of the information offered there.

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References

1. Aspartame. In: Gelman C R, Rumack B H, Hess A J, eds. DRUGDEX® System. Englewood, Colorado: MICROMEDEX, 1998. Edition expires 1999.

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United States Food & Drug Administration
Response to "Nancy Markle" Allegations
Wednesday, 13 January 1999

I have been requested by the FDA Center for Drug Evaluation and Research to respond to your request for an evaluation of the article written by Nancy Markle received via an e-mail message on the alleged toxicities of the artificial sweetener, aspartame.

My name is David Hattan and I am currently Acting Director of the Division of Health Effects Evaluation in the United States Food & Drug Administration (USFDA) Center for Food Safety and Applied Nutrition. I have worked on questions relating to the safety of aspartame repeatedly since 1978 and am familiar with the safety studies that have been conducted to support the safety of this food additive. There were well over 100 separate toxicological and clinical studies conducted to establish the safety of aspartame before it was approved for regulatory acceptance. Since its approval in 1981 by the USFDA, there have been many additional studies performed to follow up on some of the more creditable reports of aspartame- mediated adverse effects. Below I have tried to succinctly respond to certain of the allegations of toxicity proposed by Nancy Markle.

First, reports of the ingestion of aspartame in patients who later have suffered multiple sclerosis or systemic lupus is obviously not scientifically sustainable evidence that

aspartame is responsible for the occurrence of either disease. Both of these disorders are subject to spontaneous remissions and exacerbations so it is entirely possible that when patients stopped using aspartame they might have also coincidentally have had remission of their symptoms. There is no credible evidence that I am aware of that suggests that aspartame elicits multiple sclerosis or systemic lupus.

Second, the claim that aspartame ingestion results in the production of methanol, formaldehyde and formate: These claims are factual. In the gastrointestinal tract aspartame is hydrolyzed to one of its component materials, methanol, as well as the two amino acids, phenylalanine and aspartic acid. This methanol is taken up by the cells of the body and metabolized first to formaldehyde and then to formate. The key information that is missing in the description by Ms. Markle is that the levels of ingestion are very modest. In fact, there are other foodstuffs that we ingest that supply as much and sometimes even more methanol; e.g., citrus fruits and juices, and tomatoes or tomato juice. There are even higher quantities of methanol ingested when ethanol is consumed. Thus, in the final analysis this methanol is the same as from other sources and in the quantities consumed from aspartame, it is readily and naturally metabolized via the one-carbon biochemical cycle to entirely innocuous and natural body components.

Third, the claim that the two amino acids, phenylalanine and aspartic acid have neurotoxic effects. This is true in certain individuals and in high enough doses. The only subpopulation of individuals potentially susceptible to adverse effects from phenylalanine is homozygous phenylketonurics and in this case, food itself with much higher levels of phenylalanine from the protein in the diets contributes much higher toxicity for these unfortunate individuals. For those individual phenylketonurics that want to carefully control their intake levels of phenylalanine, they can do that by simply taking into consideration the amount of phenylalanine supplied by the aspartame product or, even more likely, simply refraining from use of these products. The USFDA requires that the aspartame product be labeled specially for phenylketonurics patients so that they will be aware of its presence in these products. As for the other amino acid in aspartame, the levels of aspartic acid ingested with aspartame use are many fold less than those levels responsible for causing adverse effects on the brain of animals and/or man. In fact, it is not clear that the experimentally derived data from animals is relevant to man. In any case, the levels of aspartic acid intake from aspartame are many fold below those needed to mediate neurologic effects.

Fourth, there have been numerous animal and human studies done to evaluate the possibility that aspartame causes seizures or enhances the susceptibility to seizures. In clinical studies done in adults and children with pre-existing seizures, there was no evidence of contributing to the frequency of occurrence or severity of seizures in seizure-prone individuals. There were additional studies done on seizure-prone experimental animal models to assess the possible influence of aspartame on their seizuring activity. Again, the result was the same and no influence was demonstrated on the frequency or severity of seizures.

Fifth, aspartame was comprehensively evaluated for its potential to mediate reproductive effects and birth defects. In all cases of animal testing, there was no

evidence of aspartame-mediated effects on the experimental animals at doses many times higher than those to which the human population is exposed.

Sixth, more recent allegations about aspartame mediating an increase in the incidence of brain tumors in the human population has been thoroughly refuted by both government and academic scientists.

The internet provides a convenient means of communicating information of all kinds in a potentially widespread manner. Unfortunately, the recipient of that information has no way of assessing the strength and reality of that information. There are a number of internet web sites that regularly distribute information adverse reactions supposedly mediated by aspartame that is based on anecdotal reports that cannot be confirmed. The legitimate attempts that have been made to confirm and replicate these allegations of adverse reactions from aspartame ingestion have not been successful and the USFDA continues to consider this to a be among the most thoroughly tested of food additives and that this information continues to confirm the safety of aspartame.

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