

Aspartame: A Safety Evaluation Based on Current Use Levels, Regulations, and Toxicological and Epidemiological Studies

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Evaluation Summary

Aspartame is a methyl ester of a dipeptide used as a synthetic nonnutritive sweetener in over 90 countries worldwide in over 6,000 products. Aspartame is approximately 200 times sweeter than sucrose, and can therefore add sweetness with less weight and consequently fewer calories than sugar.

Aspartame is completely hydrolyzed into three metabolites: aspartic acid, phenylalanine, and methanol. Phenylalanine enters the plasma free amino acid pool from the portal blood after partial conversion to tyrosine by hepatic phenylalanine hydroxylase. Aspartic acid is metabolized within the enterocyte. Methanol rapidly enters the portal circulation and is oxidized in the liver to formaldehyde, which is further oxidized to formic acid and then to CO₂. Formaldehyde has a half-life of about 1.5 min, so there is no accumulation in the tissue. Phenylalanine, aspartic acid, methanol and formaldehyde are all naturally present in foods and the contribution to the total daily intake of each of these from aspartame is small to trivial.

Using the most current food consumption data available for the U.S. population, the average intake of aspartame was determined to be 4.9 mg/kg bw/day (95th percentile 13.3 mg/kg bw/day in the United States). The U.S. Food and Drug Administration (FDA) established an ADI of 50 mg/kg bw for aspartame and the European Food Safety Authority recently confirmed its previously established ADI for aspartame of 40 mg/kg bw/day. Therefore, current use levels of aspartame, even by high users in special subgroups, remains well below ADI levels.

Aspartame is very stable under dry conditions, but degrades during prolonged heat treatment in aqueous solutions. Breakdown results in loss of sweetness as the breakdown products are not sweet.

The biochemical effects of aspartame consumption has been extensively studied. Parameters measured following aspartame consumption include plasma amino acid concentrations, the ratio of amino acids to other large neutral amino acids, brain neurotransmitters, plasma lipids, plasma glucose, gastrointestinal secretions, metabolizing enzymes, and other blood and urine components. The effect of co-ingestion of carbohydrates on plasma amino acid and brain neurotransmitter levels has also been studied. These biochemical changes have been measured in animal studies using various species and developmental stages, and in healthy adults and children. In addition, effects in special populations such as individuals with gastrointestinal disease, diabetes, and kidney disorders have been evaluated. In summary, consumption of large doses of aspartame in a single bolus dose will have an effect on some biochemical parameters, including plasma amino acid levels and brain neurotransmitter levels. The rise in plasma levels of phenylalanine and aspartic acid levels following administration of aspartame at doses less than or equal to 50 mg/kg bw do not exceed those observed postprandially.

Acute toxicity studies with aspartame have been conducted using oral and intraperitoneal exposure routes with mice, rats and rabbits. No deaths or adverse effects were reported with oral doses as high as 10,000 mg/kg.

In subchronic toxicity studies of aspartame, no adverse effects due to aspartame were reported in mice, rats, or dogs given doses up to 13,000, 10,000, or 6,000 mg/kg bw/day, respectively. Chronic toxicity studies with aspartame, and its

decomposition products, have been conducted in mice, rats, hamsters, and dogs. The conclusions of these studies were consistent in that no adverse effect of aspartame was found with doses up to 4,000 mg/kg bw/day.

The National Toxicology Program (NTP) completed three carcinogenicity and toxicity studies of aspartame using different transgenic mouse models. In all three studies, there were no tumors attributed to exposure to aspartame in either sex at any dose tested. In conclusion, no evidence of carcinogenicity was observed in these transgenic mouse model studies with dietary levels of aspartame equivalent to 7,500 mg/kg bw/day.

Recently, the Soffritti group reported a study of lifetime aspartame exposure in rats. The authors interpreted their findings as evidence of a carcinogenic effect. Furthermore, the authors speculated that metabolism of the methyl group in aspartame to formaldehyde may account for the carcinogenicity they claim to have observed in their experiments, but this conclusion fails to take into account the fact that the body routinely metabolizes methyl groups from many other sources. In addition, recent reevaluation of epidemiological studies of formaldehyde has revealed uncertainties in the classification of formaldehyde as a human carcinogen. Numerous expert reviews of the Soffritti reports and this panel have identified numerous potential flaws in the studies, and have concluded that the study does not provide evidence of carcinogenicity of aspartame.

The long-term studies on the toxicity of aspartame now include seven chronic studies of at least 2 years duration with mice or rats to assess carcinogenic potential and chronic toxicity, and two studies of 32 to 36 weeks duration to evaluate the tumor promotional activity of aspartame in rats. Extensive peer review and reevaluation of data and study protocols has occurred for several studies in different parts of the world. In all cases, the conclusions of the reviews by authoritative agencies, including the present Expert Panel, have been that aspartame does not have carcinogenic or cancer-promoting activity. In conclusion, it can be confidently stated that there is no credible evidence that aspartame is carcinogenic.

In addition to carcinogenicity studies, the investigation for evidence of neurologic, biochemical, behavioral and/or morphological changes following exposure to aspartame has been intensive. Studies that mimic human exposure do not show any evidence of neurological effects. The effect of aspartame on induction of seizures has been studied in rodents and primates. The studies agreed that aspartame and equimolar doses of phenylalanine are without effect on seizure susceptibility in animals, even when administered prenatally.

The majority of studies designed to detect an effect of aspartame on learning or memory have used multiple doses and multiple tests to evaluate these parameters. These studies report no effect at doses as high as 4% aspartame in the diet, even when exposure extends from conception to 90 days postnatally. Higher doses have been reported to affect various learning behaviors. In summary, well-designed studies using a range of approaches to evaluate learning and memory consistently demonstrate no effect of aspartame consumption at levels up to 4,000 mg/kg/day, indicating little likelihood that aspartame will have an effect on memory or learning in humans.

In summary, there has been extensive investigation of the possibility of neurotoxic effects due to consumption of aspartame. The data from these studies, in general, do not support the hypothesis that aspartame in the human diet will affect nervous system function, learning, or behavior. It is likely that the lack of changes in neural function in response to changes in plasma and brain amino acid levels, following even large doses of aspartame, is a reflection of the protection of brain function. This may be due to the great nutritional variation that is present in the diversity of human diets and dietary intakes.

In summary, the effect of aspartame during reproduction, development and lactation has been evaluated in rats, mice, hamsters, and rabbits. No-effect levels of exposure during reproduction and gestation have been reported to range from 1,600 mg/kg bw/day in rabbits to 4,000 mg aspartame/kg bw/day in rodents. Adverse effects on pup development were observed in rat studies when doses exceeded 5,000 mg/kg bw/day during reproduction and gestation. Consumption of up to 7,000 mg aspartame/kg bw/day during lactation had no effect on pup development or maternal health, but higher doses affected body weights. Studies evaluating the estrogenic potential of aspartame have consistently been negative. Therefore, aspartame is considered to have no reproductive or teratogenic activity, and no effect on lactation. In these studies, effects have been observed at exceedingly high doses, and were secondary to reduced body weights.

Human clinical studies with daily doses of 75 mg/kg bw/day (more than 15 times the estimated daily average intake and 1.5 times the established ADI by the FDA) of aspartame for 24 weeks were not associated with any significant changes in clinical measures or adverse effects. The effect of aspartame on behavior, cognitive function, and seizures has been studied extensively in animals, and in healthy children, hyperactive children, sugar-sensitive children, healthy adults, individuals with Parkinson's disease, and individuals suffering from depression. Overall, the weight of the evidence indicates that aspartame has no effect on behavior, cognitive function, neural function, or seizures in any of these groups.

As aspartame is attractive to diabetics as a glucose-free sweetener, testing in diabetic animal models and diabetic individuals was included in the studies submitted for aspartame approval. The conclusion of these studies is that aspartame is safe for use by diabetics, including those with chronic renal failure, and may aid diabetics in adhering to a sugar-free dietary regime.

Recently, a meta-analysis of 16 randomized, controlled trials assessing the effect of aspartame consumption on weight loss, weight maintenance, and energy intake was conducted. There is no evidence to support an association between consumption of aspartame and the development of obesity. On the contrary, when used in multidisciplinary weight control programs, aspartame may actually aid in long-term control of body weight.

Epidemiological studies on aspartame include several case-control studies and one well-conducted prospective epidemiological study with a large cohort ($n = 473,984$), in which the consumption of aspartame was measured. The studies provide no evidence to support an association between aspartame and brain or hematopoietic tumor development.

This evaluation summary highlights the major issues regarding aspartame safety. Several other potential effects associated with consuming aspartame, which have been described since its introduction to the market, have also been reviewed and evaluated in this document. These other potential effects were considered to be either of little biological significance (such as a small change in enzyme activity), or the available evidence available at this time is not adequate to conclude that the reported effect actually exists or is due to aspartame; therefore, these other effects are not included in the evaluation summary. The reader is encouraged to refer to the body of this review to obtain a comprehensive understanding of the science relating to aspartame safety.

The current weight of evidence is that aspartame is safe at current levels of consumption as a nonnutritive sweetener. Consumption remains well below established ADI levels, even among special high user sub-populations. No credible evidence was found that aspartame is carcinogenic, neurotoxic, or has any other adverse effect on health when consumed even at levels many times the established ADI levels.

Conclusions

Aspartame's metabolism is well understood and follows that of other common foods. Aspartame consumption, even at levels much higher than that expected under typical circumstances, has virtually no impact on levels of other blood constituents such as amino acids, methanol or glucose.

Aspartame is a well-studied sweetener whose safety is clearly documented and well established through extensive laboratory testing, animal experiments, epidemiological studies, and human clinical trials.

Controlled and thorough scientific studies confirm aspartame's safety and find no credible link between consumption of aspartame at levels found in the human diet and conditions related to the nervous system and behavior, nor any other symptom or illness.

Aspartame is well documented to be nongenotoxic and there is no credible evidence that aspartame is carcinogenic. Aspartame does not increase hunger in those that use it; to the contrary, studies indicate it might be an effective tool as part of an overall weight management program.

Aspartame is a well-characterized, thoroughly studied, high-intensity sweetener that has a long history of safe use in the food supply and can help reduce the caloric content of a wide variety of foods.