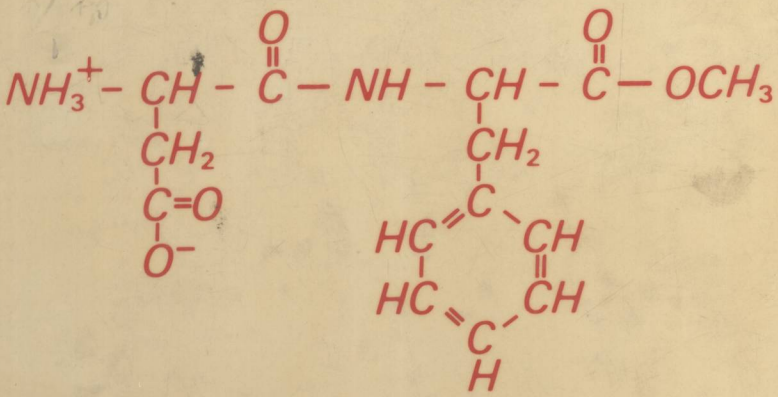
ASPARTAME

Physiology and Biochemistry

edited by

Lewis D. Stegink • L. J. Filer, Jr.



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ASPARTAME

FOOD SCIENCE AND TECHNOLOGY

A Series of Monographs and Textbooks

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Preface

Aspartame may be the most thoroughly studied food additive ever approved by the U.S. Food and Drug Administration (FDA) in terms of research studies conducted prior to approval. Safety studies of aspartame were started in the late 1960s, when only the more classical toxicologic testing was required. These studies, however, extended into the 1970s, as more rigorous tests were required by both regulatory agencies and consumer groups. During these two decades, aspartame faced and survived a number of regulatory reviews (see Commissioner's summary in *Federal Register* 46, 38285, 1981). This book summarizes in part the research that resulted in aspartame's approval as a food additive as well as related topics regarding its function as a potential sweetening agent.

The sweet taste of aspartame was discovered serendipitously in 1965, a story described by Mazur in Chapter 1. Interestingly, this discovery opened up an entirely new area in the study of chemical structure and its relationship to taste. Indeed, as discussed by Schiffman, aspartame's taste was a sweet surprise, remarkably clean, very much like that of sucrose, and free of a metallic aftertaste.

Following the discovery of aspartame, Searle petitioned the FDA for approval to market it as a sweetening agent in certain foods (*Federal Register* 38, 5921, 1973). Searle's petition provided a large volume of data in support of claims for safety. Some of these studies are summarized by Molinary, Ishii, Bryan, Koestner, Cornell et al., Sturtevant, and Visek.

On July 26, 1974, the FDA approved Searle's petition and issued a regulation authorizing the use of aspartame in certain foods and for certain technologic purposes (*Federal Register* 39, 27317, 34520, 1974). As permitted by law, two parties formally objected to the regulation and requested a formal evidentiary hearing. The objections filed by Olney, and jointly by Turner and Label Inc., questioned the safety of the aspartic acid and phenylalanine moieties of as-

partame. Later these parties waived their right to a formal evidentiary hearing conditioned upon the establishment of a Public Board of Inquiry (PBOI) composed of three qualified scientists from outside the FDA to review and evaluate the issue of safety. This novel approach represented a first as a means for resolving questions of food safety. Olney's concern was later expanded to include questions about a possible role of aspartame (or its diketopiperazine conversion product) in the induction of brain tumors in rats.

Before a PBOI could be convened, preliminary results from an FDA audit of the records of certain animal studies indicated the need for a comprehensive review of some aspartame research data. Thus the FDA formally stayed the regulation authorizing the marketing of aspartame (*Federal Register* 40, 56907, 1975). With the knowledge and approval of Searle, the aspartame data in 15 pivotal studies were thoroughly audited by either the FDA or the Universities Associated for Research and Education in Pathology, Inc. (UAREP). This massive undertaking required two years to complete. At the end of this review, both the FDA and UAREP agreed that the studies were authentic, and the FDA turned its attention to arranging the PBOI. During this interval, Searle carried out a large number of human and animal studies to further evaluate the safety of aspartame. Chapters by Ishii, Applebaum et al., Reynolds et al., Suomi, Stegink, Baker, Pitkin, Filer et al., and Koch and Wenz summarize these investigations.

In late January 1980, the Public Board of Inquiry heard three full days of testimony. Posthearing briefs and/or rebuttal statements were filed by all parties. On October 1, 1980 the PBOI issued its decision. The PBOI agreed with Searle and the FDA that the aspartate and phenylalanine content of aspartame did not constitute a risk when the additive was used according to the petition. However, the PBOI agreed with Olney that available data did not rule out the possibility that aspartame or its diketopiperazine caused brain tumors in rats. Accordingly, the Board withdrew approval of G. D. Searle & Co.'s food additive petition, and after vacating the stay on the aspartame regulation (21 CFR 172.804), revoked that regulation in its entirety.

Olney, Searle, and the FDA all filed detailed exceptions to those portions of the PBOI decision in which the PBOI disagreed with their respective positions. Turner also filed an exception, objecting to the scope of evidence considered by the PBOI. As a result, the FDA made a detailed reevaluation of the data considered by the PBOI, particularly the data relating to the brain tumor issue. Some of the brain tumor data reevaluated are reviewed in chapters by Ishii, Koestner, and Cornell et al. After considerable review of available data, a process that also included examination of new data (detailed in *Federal Register* 46, 38285, 1981), the Commissioner determined that aspartame had been shown to be safe for its proposed uses as a food additive and approved the food additive petition. Aspartame was later approved for use in beverages (*Federal Register* 48, 21378, 1983).

Just as this book is going to press, additional theoretical questions are being raised about the capacity of aspartame to affect brain neurotransmitter levels and behavior (*New England Journal of Medicine* 309, 429, 1983). Although

these claims are not specifically addressed in this book, possible behavioral effects of aspartame are discussed in chapters by Butcher et al., Molinary, Reynolds et al., and Suomi. Fernstrom's chapter addresses the brain neurotransmitter issue.

The book is divided into five major sections: (1) the history and background of aspartame, (2) the metabolism of its component parts, (3) sensory and dietary aspects of the compound, (4) preclinical studies of aspartame and its diketopiperazine, and (5) clinical studies in man or nonhuman primates that address specific questions related to its food use.

In the first section Mazur describes its serendipitous discovery and Inglett discusses aspartame in relation to other sweeteners. Since aspartame is a dipeptide methyl ester (L-aspartyl-L-phenylalanine methyl ester), David Matthews was asked to prepare a chapter on the hydrolysis and absorption of peptides. Since orally ingested aspartame releases aspartate, phenylalanine, and methanol to portal blood, the metabolism of each of these components is discussed in chapters by Stegink, Harper, and Tephly and McMartin. The chapter by Tephly and McMartin also addresses the issue of potential methanol toxicity. Animal studies on the metabolism and distribution of radioactively labeled aspartame are described in chapters by Oppermann and by Matsuzawa and O'Hara.

The sensory and dietary aspects of aspartame are discussed in chapters by Schiffman and by Roak-Foltz and Leveille. The chapter by Schiffman reviews taste and taste perceptions of aspartame and other sweeteners. The review by Roak-Foltz and Leveille examines how projected intakes of aspartame might affect normal dietary intake of aspartate, phenylalanine, and methanol. Homler discusses specific problems that aspartame presents to the food scientist in new product formulation. Bowen discusses possible benefits of artificial sweeteners in preventing dental caries, and Porikos and Van Itallie discuss the value of aspartame in weight reduction.

The summary of preclinical studies includes a review of G. D. Searle & Co.'s chronic animal feeding studies by Molinary. Ishii reviews similar studies carried out in Japan. Bryan discusses the potential of sweetening agents to produce bladder cancer. Since dicarboxylic amino acids are known to cause brain damage in the infant rodent, Applebaum et al. discuss aspartate neurotoxicity in the rodent and Reynolds et al. describe neurotoxicity studies of aspartame in the infant nonhuman primate. The relative risk of the phenylalanine content of aspartame is discussed in chapters by Butcher and Vorhees, Reynolds et al., and Suomi. One major issue at the PBOI was the relationship of aspartame to brain tumors in rats fed large doses of the compound. This aspect of safety is discussed in chapters by Ishii, Koestner, and Cornell et al. This section is concluded by a chapter prepared by Sturtevant on possible neurohormonal effects of aspartame ingestion.

Specific issues relating to human consumption of aspartame are summarized in a series of chapters. Studies of chronic ingestion of aspartame carried out prior to the PBOI are summarized by Visek. Stegink discusses an extensive series of acute dosing studies in humans with aspartame carried out to resolve questions

of safety relative to aspartate, phenylalanine and methanol content. Baker discusses the possible effects of aspartame ingestion on the amino acid composition of human milk, and Pitkin discusses aspartame ingestion during pregnancy. The question of whether the human infant metabolizes aspartame as effectively as adult subjects is resolved in a chapter by Filer et al., while Koch and Wenz discuss the use of aspartame by individuals homozygous or heterozygous for phenylketonuria.

The potential for interaction between aspartame and monosodium glutamate is reviewed by Stegink. The use of aspartame by diabetics is discussed by Horwitz. Finally, Fernstrom discusses possible interactions of aspartame with prescription drugs and considers the question of whether aspartame ingestion affects brain neurotransmitter concentrations. Food additives proposed for FDA approval face a more rigorous review today than compounds approved in past years. The extensive research program carried out to demonstrate aspartame safety may serve as a new standard for the study of food additives.

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