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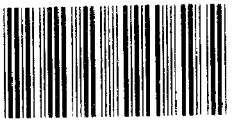
GAO

Report to the Honorable
Howard M. Metzenbaum, U.S. Senate

June 1987

FOOD AND DRUG ADMINISTRATION

Food Additive Approval Process Followed for Aspartame



GAO/HRD-87-46

GAO

United States
General Accounting Office
Washington, D.C. 20548

Comptroller General
of the United States

B-223552

June 18, 1987

The Honorable Howard M. Metzenbaum
United States Senate

Dear Senator Metzenbaum:

At your request, we have reviewed the Food and Drug Administration's (FDA's) process for approving aspartame—a sweetener marketed under the brand name NutraSweet®. This report discusses FDA's (1) process for approving aspartame, (2) review of the scientific issues raised concerning the aspartame studies, and (3) monitoring of current safety concerns on aspartame.

We did not evaluate the scientific issues raised concerning the studies used for aspartame's approval or FDA's resolution of these issues, nor did we determine aspartame's safety. We do not have such scientific expertise. However, we did send a questionnaire to researchers to obtain their views on aspartame's safety and information on aspartame's research. These results are included in this report.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from its issue date. At that time, we will send copies to the Secretary of Health and Human Services; the Commissioner of FDA; the Director, Office of Management and Budget; The NutraSweet Company; Mr. James Turner, Community Nutrition Institute; and other congressional committees and interested parties. We will also make copies available to others on request.

Sincerely yours,

Milton J. Socolar

Acting Comptroller General
of the United States

Executive Summary

Purpose

Since 1974, aspartame, a food additive marketed under the brand name NutraSweet®, has been the subject of controversy. Concerns have been raised about the quality of the research supporting its safety and the long-term effects that increased consumption could have on the public.

As a result of these controversies, Senator Howard M. Metzenbaum requested GAO to investigate the Food and Drug Administration's (FDA's) approval of aspartame in 1981. GAO determined

- if FDA followed its required process in approving aspartame in dry foods,
- if FDA addressed questions raised on aspartame research,
- the FDA Commissioner's basis for reapproving aspartame in 1981, and
- how FDA is addressing current safety concerns on aspartame.

GAO sent a questionnaire to 96 scientific researchers to obtain their views on aspartame's safety and information on aspartame research.

Background

G.D. Searle and Co. began developing aspartame, a sweetener, in 1965. However, before it could be marketed, Searle had to submit research studies to FDA to demonstrate aspartame's safety. The Food, Drug, and Cosmetic Act's legislative history and implementing regulations define safety to mean a reasonable certainty that the use of a food additive is not harmful. Scientists emphasized the scientific impossibility of proving the absolute harmlessness of any chemical.

Although aspartame was originally approved for use in dry foods in 1974, not until 1981 was Searle permitted to begin marketing it. In the 7 intervening years, FDA had to resolve questions raised concerning the quality of Searle's studies, aspartame's safety, and the need for additional research. Since 1981, FDA has approved additional uses of aspartame, including carbonated beverages.

Results in Brief

FDA adequately followed its food additive approval process in approving aspartame for marketing by reviewing all of Searle's aspartame studies, holding a public board of inquiry to discuss safety issues surrounding aspartame's approval, and forming a panel to advise the Commissioner on those issues. Furthermore, when questions were raised about the Searle studies, FDA had an outside group of pathologists review crucial aspartame studies.

Throughout aspartame's approval history, GAO found that FDA addressed safety issues raised internally and by outside scientists and concerned citizens.

For example:

- FDA addressed the safety concerns raised during its review of Searle's aspartame studies and used these studies to establish the safe level for long-term consumption (Acceptable Daily Intake) before approving aspartame for marketing.
- Although a 1975 investigative task force identified problems with the quality of certain aspartame studies, FDA's actions to substantiate the accuracy and reliability of those studies were appropriate.
- The former FDA Commissioner's final decision approving aspartame addressed the various scientific issues questioned by a public board of inquiry decision and outlined why additional research on aspartame's safety was not needed. Members of a Commissioner's advisory panel told GAO that their concerns and the issues raised by the board were adequately explained to the Commissioner before his decision.

However, GAO did not evaluate the interpretation of the scientific issues raised or the adequacy of FDA's resolution of issues on the studies used for aspartame's approval, nor did it determine aspartame's safety; GAO does not have such expertise.

Twelve of the 69 scientists responding to GAO's questionnaire expressed major concerns about aspartame's safety. However, FDA and others have sponsored over 70 completed, ongoing, and planned studies on aspartame, including its effects on neurological behavior, children, and pregnant women.

GAO believes that FDA's and other scientists' planned and ongoing research, and FDA's monitoring of adverse reactions, should provide FDA with a basis for determining what future actions, if any, are needed on aspartame.

Principal Findings

FDA's Approval Process

Searle submitted nearly 170 studies or analyses to support aspartame's safety. FDA considered seven of these studies crucial to aspartame's

approval in dry foods. GAO believes that these crucial studies met FDA's requirements for the types of studies needed for a food additive approval. FDA reviewed all of the studies submitted and concluded that they demonstrated aspartame's safety.

Quality of Searle's Studies

In 1975, an FDA task force investigating Searle laboratory practices questioned the quality of the data in certain aspartame studies. The task force concluded that in some Searle studies, it was difficult to draw conclusions on safety.

As a result of the task force's findings, detailed investigations of 15 aspartame studies, including the 7 crucial studies, were begun in 1977 by FDA and a group of university pathologists. After reviewing 12 Searle aspartame studies, the university pathologists noted that although they found a number of minor discrepancies in the studies, there were few, if any, discrepancies that would significantly affect the studies' results. For the remaining three studies, FDA stated that data problems noted would not alter the conclusions. FDA concluded that the studies were of sufficient quality to be used to assess aspartame's safety.

Commissioner's Decision

In early 1980, a public board of inquiry composed of three university scientists heard scientific discussions relating to aspartame's effects on the brain. The board concluded that aspartame did not cause brain damage but believed the aspartame studies did not conclusively show aspartame did not cause brain tumors. The board used its authority and revoked FDA's 1974 aspartame approval and decided additional research was needed before aspartame could be marketed.

A panel of FDA scientists and a lawyer were selected to advise the former Commissioner on the issues discussed by the board. Three of the five panel members reviewing the brain tumor issue did not believe Searle's studies conclusively showed aspartame did not cause brain tumors.

The panel briefed the Commissioner on the issues concerning aspartame's safety, and on July 18, 1981, the Commissioner overturned the board's decision and reapproved aspartame for use in dry foods. The Commissioner concluded there was reasonable certainty aspartame did not cause brain tumors. He said that he was persuaded by the data that aspartame should be approved. GAO did not find any evidence that pressure was put on the former FDA Commissioner to approve aspartame.

Current Concerns on Aspartame

FDA monitors aspartame's safety through reported adverse reactions and market research surveys that provide data on aspartame consumption. FDA has analyzed about 3,000 reported adverse reactions. However, FDA concluded that it cannot definitely state whether aspartame is or is not associated with the reported reactions. Most of the reactions reported are mild or moderate, such as headache and dizziness. The market surveys show consumption is far below the Acceptable Daily Intake set by FDA. The data have shown that, based on body weight, the highest consumers of aspartame are in the 0- to 23-month-old group. For example, an individual in this group consuming aspartame at the highest reported level would ingest aspartame at about 40 percent of FDA's Acceptable Daily Intake. In a 22-pound child, the amount of aspartame established as the Acceptable Daily Intake is equivalent in sweetness to 25 teaspoons of sugar daily.

In GAO's questionnaire, 28 out of 69 scientists indicated areas where they believed more research is needed on aspartame to resolve their concerns. The areas most frequently mentioned were neurological functions, brain tumors, seizures, headaches, and adverse effects on children and pregnant women. Research is ongoing in all of these areas except for brain tumors. FDA stated that it believed aspartame was shown to be safe and therefore more research in these areas, although useful, is not needed to demonstrate its safety.

Recommendations

Because FDA followed its required process in approving aspartame and monitors adverse reactions and ongoing aspartame research, GAO is making no recommendations.

Agency and Other Comments

The Department of Health and Human Services and The NutraSweet Company, the current manufacturer of aspartame, were in general agreement with the report's findings. However, The NutraSweet Company commented that the results of the GAO questionnaire on aspartame's safety were not representative of prevailing scientific opinion. GAO recognizes that the results of its questionnaire may not be totally representative of scientific opinion. However, GAO believes the questionnaire results provide useful information on ongoing aspartame research.

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Abbreviations

CFSAN	Center for Food Safety and Applied Nutrition
DKP	Diketopiperazine
FDA	Food and Drug Administration
GAO	General Accounting Office
PBOI	Public Board of Inquiry
PKU	Phenylketonurics
UAREP	Universities Associated for Research and Education in Pathology

Introduction

Aspartame, a sweetener and flavor enhancer marketed under the brand name NutraSweet®, is currently used in over 150 food products in the United States and, according to The NutraSweet Company, marketed in food products in 29 foreign countries. Since first approved in 1974, aspartame has been surrounded by controversy. Consumer organizations raised concerns about its safety. Research scientists have questioned whether it adversely affects brain chemistry and are now concerned that increased consumption by the public could have long-term health effects. The Food and Drug Administration (FDA) contends that aspartame is one of the most tested food additives in U.S. history, with more than 100 animal and human studies supporting its safety. As a result of these controversies, Senator Metzenbaum requested that we review FDA's process for approving aspartame and its handling of the related scientific issues.

What Is Aspartame?

G.D. Searle and Co.[1] began developing aspartame—a sweetener about 180 times as sweet as sugar—in 1965. It is a white, odorless, crystalline powder composed of 2 amino acids[2]—L-aspartic acid and L-phenylalanine. Like sugar, aspartame produces about 4 calories per gram. However, because aspartame is sweeter than sugar, it provides only a fraction of the calories provided by a quantity of sugar yielding equivalent sweetness.

Currently, aspartame is approved for use as a sweetener in

- dry, free-flowing sugar substitutes for table use in package units not to exceed the sweetening equivalent of two teaspoonfuls of sugar;
- sugar substitute tablets for sweetening hot beverages;
- cold breakfast cereals;
- chewing gum;
- dry bases for beverages, instant coffee, gelatins, puddings, fillings, and dairy product analog (imitation whipped cream) toppings;
- carbonated beverages and carbonated beverage syrup bases;
- chewable multivitamins;
- noncarbonated frozen or refrigerated, concentrated and single-strength fruit juices, fruit drinks, fruit-flavored drinks and ades, and imitation fruit-flavored drinks and ades, and also frozen stick-type confections;
- breath mints; and

[1]In 1985, G.D. Searle and Co. was sold to Monsanto Company, and the division that handles aspartame became The NutraSweet Company.

[2]Amino acids form the chief structure of proteins; several of them are essential in human nutrition.

- tea beverages to include ready-to-serve, liquid concentrates, and dry bases.

Regulation of Food Additives

The Food Additives Amendment of 1958 (Public Law 85-929), which amended the Federal Food, Drug, and Cosmetic Act, requires FDA, in response to a petition for approval of a proposed use of a food additive, to establish regulations prescribing conditions for safe use of the food additive or to deny the food additive's use. A food additive is a substance intentionally used that becomes or may become a component of food or otherwise affect its characteristics. Food additive regulations can be amended to include new uses of the additive or can be repealed based on new data.

Any person may file a petition with FDA proposing the issuance of a food additive regulation. The petition must contain

- the name and all pertinent information concerning the food additive, including, where available, its chemical identity and composition;
- a statement of the conditions of the additive's proposed use, including all directions, recommendations, and suggestions for its proposed use, and its proposed labeling;
- all relevant data on the physical or other technical effects the additive is intended to produce and the quantity of the additive required to produce such effects;
- a description of practical methods for determining the quantity of the additive in or on food and any substance formed in or on food because of its use; and
- full reports of investigations made about the additive's safety, including full information on the methods and controls used in conducting the investigations.

FDA's Center for Food Safety and Applied Nutrition (CFSAN), formerly the Bureau of Foods,[3] is responsible for evaluating the safety of food additives. In determining safety, the act (21 U.S.C. 348(c)(5)) requires FDA to consider

- the additive's probable consumption and any substance formed in or on food by its use;

[3]In 1982, FDA reorganized; at that time, the Bureau of Foods became CFSAN, and the Bureau of Drugs and the Bureau of Biologics became the Center for Drugs and Biologics. In this report, we refer to the bureaus by their current names.

- the additive's cumulative effects in the diets of humans or animals, taking into account any chemically or pharmacologically related substance or substances in the diets; and
- safety factors generally recognized by qualified experts as appropriate for the use of animal experimentation data.

The Federal Food, Drug, and Cosmetic Act does not specifically define safety. However, the legislative history of the Food Additives Amendment indicates that safety means, "proof of a reasonable certainty that no harm will result from the proposed use of an additive." During hearings on the amendment, testimony was provided emphasizing the impossibility of proving, within the bounds of scientific knowledge, the absolute harmlessness of any chemical substance. Consistent with the legislative history, implementing regulations define safety as a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.

The safety assessment of a substance is usually based on animal studies submitted by the petitioner. In these studies, animals are divided into groups. The diet of one group (the control group) does not contain the substance in question. The other groups are fed varying dose levels of the substance. The dosed and control groups are compared to identify the substance's potential effects. In addition, statistical tests are used to determine the significance of any differences between the dosed and control groups.

A Brief History of Aspartame's Approvals

Although FDA approved aspartame for use in dry foods in 1974, it was not until 1981 that Searle could begin marketing aspartame because of questions concerning aspartame's safety and Searle's research practices. In 1983, aspartame was approved for use in carbonated beverages. Table 1.1 identifies key events in aspartame's history that are discussed in more detail in later chapters.

Table 1.1: History of Aspartame's Approvals

Date	Event
February 1973	Searle submitted a petition for aspartame's use in all foods.
July 1974	FDA approved aspartame's use only in dry foods.
August 1974	Objections were filed on aspartame's approval, and two objectors requested a hearing on aspartame's safety.
July 1975	The FDA Commissioner appointed a task force to investigate Searle's animal studies on seven products, including aspartame. This on-site investigation was to determine if Searle submitted false information to FDA.
November 1975	The objectors to aspartame's approval agreed to a Public Board of Inquiry (PBOI) to hear safety concerns.
December 1975	The task force concluded that some of Searle's studies were questionable; therefore, FDA stayed the aspartame regulation—aspartame could not be marketed. The PBOI was delayed because of problems noted in Searle's studies.
July 1976	In response to the task force findings, FDA decided to investigate aspartame studies to determine whether FDA could rely on these studies to assess aspartame's safety.
April 1977	An FDA team began investigating three aspartame studies.
August 1977	Universities Associated for Research and Education in Pathology (UAREP) began investigating 12 aspartame studies.
March 1979	CFSAN concluded that the deficiencies found in both the FDA and UAREP reviews were not significant enough to invalidate Searle's aspartame studies. FDA decided the PBOI could now be convened.
January 1980	The PBOI held hearings on the objections to aspartame's 1974 approval.
October 1980	The PBOI revoked aspartame's 1974 approval, concluding that more studies were needed to determine whether aspartame caused brain tumors.
March 1981	An FDA Commissioner's panel was established to review issues raised by the PBOI.
July 1981	The panel did not reach a consensus on aspartame's safety but outlined the issues. The Commissioner overturned the PBOI decision and reapproved aspartame, allowing it to be marketed in dry foods.
July 1983	FDA approved aspartame's use in carbonated beverages.
August 1983	Objectors to aspartame's approval in beverages requested that FDA stay the carbonated beverage regulation and hold a hearing on aspartame's safety. FDA later denied these requests.
December 1983	Objectors filed suit in federal district court to require FDA to hold a hearing and to stay both dry foods and beverages approvals.
April 1984	After the district court dismissed the objectors' suit, saying it lacked jurisdiction, the objectors petitioned for the U.S. court of appeals to review the dismissal and FDA's denial of a hearing.
May 1984	FDA approved aspartame's use in multivitamins.

Date	Event
April 1986	After the court of appeals decided against the objectors, the Supreme Court declined to hear the case appealed by objectors.
July 1986	Objectors petitioned FDA to repeal the dry foods and carbonated beverages regulations.
November 1986	FDA denied the objectors' petition. FDA approved aspartame's use in fruit juices, stick-type confections, breath mints, and iced tea. The following month an objector petitioned FDA to stay these regulations and requested a public hearing.
December 1986	FDA declared aspartame safe for use as an inactive ingredient in drugs provided the labeling meets certain specifications.
January 1987	One objector petitioned the court of appeals to review FDA's November 1986 denial of his petition.

Objectives, Scope, and Methodology

In May 1985, Senator Howard M. Metzenbaum requested that we review FDA's approval of aspartame.[4] Specifically, Senator Metzenbaum noted that (1) the 1975 FDA task force raised questions about Searle's testing procedures, (2) a PBOI recommended aspartame not be approved for marketing, and (3) three FDA scientists advising the Commissioner recommended against approval. In addition, the Senator's office gave us a list of specific questions he wanted us to address during our review. These questions included:

- How many Searle studies did FDA use to determine aspartame's safety, what clinical studies did Searle submit, and how did FDA resolve problems it identified with the studies? (See ch. 2.)
- How was UAREP's task defined, and was Searle involved in contracting with UAREP? (See ch. 3.)
- How could FDA rely on Searle's animal studies after the 1975 task force, FDA team, and UAREP found problems with the studies, and how were such problems resolved? (See ch. 3.)
- Should the PBOI have addressed the quality of Searle's studies and aspartame's use in carbonated beverages? (See ch. 4.)
- How did the FDA Commissioner consider the views of panel members, what effect did a study conducted in Japan have on the Commissioner's decision to approve aspartame in dry foods, and was the White House involved in the decision? (See ch. 5.)
- Before approving aspartame's use in carbonated beverages, did FDA evaluate its effects on the brain and what studies were used to raise the acceptable daily consumption set by FDA? (See ch. 6.)

[4]In response to part of this request, on July 22, 1986, we issued a briefing report (GAO/HRD-86-109BR), which contained information on six former Department of Health and Human Services employees and their involvement in the approval of aspartame.

While addressing these questions, our overall objectives were to determine whether FDA

- followed its required process in approving aspartame,
- addressed the questions raised on the aspartame studies, and
- is monitoring and addressing current safety concerns on aspartame.

Since our objectives were to review FDA's actions relating to aspartame's approvals and current monitoring, our review focused on pertinent FDA files and officials. FDA's files contained the basis for FDA's approvals of aspartame, including Searle's studies, correspondence, and memoranda indicating FDA's and Searle's resolution of identified problems, and the information used by the PBOI to make its decision on aspartame's safety. In addition, we contacted UAREP officials and PBOI participants to obtain information on their reviews of aspartame studies, and we contacted The NutraSweet Company for information on its recent research on aspartame.

We performed our review between July 1985 and February 1987 in accordance with generally accepted government auditing standards.

To achieve our objectives, we reviewed records contained in FDA's:

- Division of Management Services' chronological files on Searle for January 1964 to July 1985. These files include correspondence and memos of meetings and telephone contacts between FDA and Searle officials on Searle products regulated by FDA.
- CFSAN files on aspartame. These files contain the animal and clinical studies submitted by Searle since 1969 on aspartame and correspondence relating to such studies.
- Docket Management Branch files on aspartame. These are the official files supporting FDA's decision to approve aspartame. They also contain information used by the PBOI.
- Freedom of Information files on the 1975 task force review of Searle's studies.

At CFSAN, we reviewed files to identify and categorize the studies submitted by Searle, determine whether CFSAN had reviewed each study, and identify the studies crucial to the approval of aspartame. CFSAN confirmed our list of crucial studies and the categorization of them. (See ch. 2.)

We also reviewed FDA's regulations and guidance pertaining to aspartame's approval. We talked with FDA and Department of Health and Human Services officials involved in the approval and the current monitoring efforts of aspartame's safety and consumption. We also contacted key former FDA officials involved in the approval of aspartame, including one former commissioner and one former acting commissioner. In addition, we interviewed participants in the UAREP and FDA review of Searle's studies, the team leader and other members of FDA's 1975 task force, two members of the PBOI (the third member was very ill at the time of our review), eight members who served on the Commissioner's panel, and the two objectors who requested the PBOI on aspartame's approval in dry foods.

We contacted MRCA Information Services and obtained permission to use its data on the current consumption of aspartame in our report. CFSAN reviews information from MRCA to monitor aspartame's consumption.

We did not evaluate the interpretation of scientific issues on the studies used for aspartame's approval, nor did we determine aspartame's safety; we do not have the necessary expertise. We discussed how best to resolve the scientific issues with researchers inside and outside of FDA, including officials from the National Academy of Sciences, the National Cancer Institute, and the National Toxicology Program. In general, these researchers advised us that it would be better to conduct new studies that address the scientific issues on the safety of aspartame than reevaluate Searle's studies. Most of Searle's studies were conducted before FDA issued regulations setting standards for laboratory research.

As a result, we sent a questionnaire to 96 researchers to obtain their views on aspartame's safety and current research on aspartame (see app. I). We identified these researchers through FDA officials and files, a literature search on aspartame, and referrals from other researchers. We limited the questionnaire to people doing research in the United States and included only information from studies using aspartame. Because we could not identify all researchers who have performed studies on aspartame, we do not know if the results of the survey are representative of the scientific community. When agreed to by the respondent, we gave the study information to CFSAN.

Of the 96 researchers sent a questionnaire,

- 69 responded,

- 7 said another researcher would provide us the information or refused to answer the questionnaire,
- 11 said the questionnaire was not applicable to them,
- 1 had moved and could not be located, and
- 8 did not respond.

We sent 4 of the 96 questionnaires to The NutraSweet Company in-house researchers. The company refused to let them participate because it did not want to be accused of biasing the results. However, it gave us a list of its completed and ongoing research on aspartame.

FDA Approved Aspartame's Use in Dry Foods

In 1973, Searle submitted a petition for aspartame's use as a food additive. At that time, FDA did not have published guidelines outlining the types of animal studies that needed to be conducted to support food additives. Instead, CFSAN informed Searle of the types of studies needed to support a safety assessment of aspartame for use as a nutritive sweetener in all foods.

Searle submitted to FDA 168 studies or analyses to support aspartame's safety. It submitted 119 of these studies before FDA's 1974 approval of aspartame in dry foods. While many of the studies submitted were not required, CFSAN considered seven of them crucial to determining aspartame's safety in dry foods. These crucial studies met CFSAN's requirements for direct food additives.

CFSAN reviewed all 168 studies and expressed concern over a number of issues. During its review of aspartame studies, CFSAN asked Searle to perform additional studies or analyses; in others, CFSAN obtained independent evaluations of the data. Although CFSAN concluded that Searle studies established the safe use of aspartame in dry foods, it concluded additional studies were needed before aspartame could be used in other foods, such as carbonated beverages.

Searle's Aspartame Petition Met FDA's Requirements

Food additive petitions must contain general information describing the food additive and include reports of scientific studies conducted to demonstrate the proposed additive's safety. However, in 1974, FDA did not have written guidelines describing the types of studies required to show a food additive's safety and instead determined such requirements on a case-by-case basis. Searle met FDA's petition filing and study submission requirements for food additives.

FDA Had No Written Guidelines in Early 1970's for Food Additive Studies

On February 9, 1973, Searle submitted a petition to FDA for aspartame's use in foods as a ". . . nutritive sweetener with flavoring enhancing properties." Aspartame's proposed uses included dry beverage mixes, gelatins, puddings, fillings, whipped toppings, presweetened breakfast cereals, chewing gums, tabletop sweeteners, and carbonated beverages. Searle's petition contained general information on the characteristics and specifications of aspartame, its proposed uses, and summaries of scientific animal and human studies regarding its safety.

Although the Federal Food, Drug, and Cosmetic Act and its implementing regulations outline information that should be contained in a

food additive petition (see ch. 1), they do not specify the type of studies required to show the safety of food additives. Since FDA had no written guidelines describing required safety studies in 1974, CFSAN officials followed broad guidelines, published by scientific organizations. These guidelines provided very general information on topics of concern and safety considerations related to the review of chemicals used in foods, drugs, and cosmetics. CFSAN identified more specific requirements based on the individual safety-testing needs of each additive under review.

In 1977, CFSAN issued a memo outlining types of studies needed for different food additives. In 1982, CFSAN published guidelines for the safety assessment of food additives. CFSAN officials told us this book, known as the "Red Book," formalized food additive guidelines that had been informally followed in prior years. The Red Book set standards for the types of studies required to demonstrate safety and provided criteria to be used in conducting safety studies. It also gave CFSAN the flexibility to adjust study requirements to reflect the need for more rigorous testing on some additives.

As shown in table 2.1, our comparison of requirements for direct food additives, such as sweeteners, as outlined in the CFSAN memo and the Red Book, showed no major differences.

Table 2.1: CFSAN's Toxicity Study Requirements for Direct Food Additives

1977 CFSAN memo	1982 Red Book[a]
Lifetime feeding study (about 2 years) in a rodent species with in-utero exposure for carcinogenesis and chronic toxicity	Lifetime carcinogenicity and chronic feeding study[b] in one rodent species[c]
Lifetime feeding study (about 2 years) in a rodent species for carcinogenesis[d]	Lifetime carcinogenicity study in another rodent species[d]
Short-term feeding study (about 6 months to 1 year) in a nonrodent species	Long-term (at least 1 year) feeding study in nonrodent species
Multigeneration reproduction feeding study with teratology[e] phase	Multigeneration reproduction study with teratology phase

[a]The Red Book also lists short-term studies for carcinogenic potential as a requirement. However, an FDA official told us that these studies are not required because long-term studies are used to more completely evaluate toxicological issues.

[b]This study is usually conducted as a carcinogenicity/chronic toxicity test.

[c]CFSAN officials told us in the case of direct food additives, such as sweeteners, in-utero exposure is required in this study.

[d]A CFSAN official told us CFSAN began requiring lifetime studies in two different rodent species during the mid-1970's.

[e]The study of abnormal development and congenital malformations.

CFSAN Considered Nine Studies Crucial to Aspartame's Approval

Searle submitted to FDA 168 studies or analyses to support aspartame's safety; it submitted 119 of these before FDA's 1974 approval of aspartame. Table 2.2 categorizes these studies or analyses by type.

Table 2.2: Searle's Studies Submitted on Aspartame

Type of study	Definition	Number of studies submitted
Toxicological	Animal studies to determine the relationship between dose of a substance and any adverse effects. These studies evaluate effects from both long-term repeated and high single consumption. The food additive requirements fit into this category.	89
Pharmacological	Studies to determine the therapeutic value of a substance. These studies are normally not submitted for a food additive.	25
Metabolic	Studies to determine how a substance is handled in the living body.	29
Clinical	Human metabolic and toxicological studies. Human studies are not required for food additives.	25
Total		**168**

Many of the 168 studies were not required for approval, but Searle submitted all completed aspartame studies. These studies gave CFSAN further information on aspartame's overall effects and helped in the design of the more important long-term studies. For example, Searle used a number of short-term studies to develop the most desirable dose ranges for long-term studies. In addition, Searle conducted several mutagenicity studies[1] to obtain a preliminary indication of aspartame's carcinogenic potential. CFSAN officials told us mutagenicity studies are conducted before long-term studies because they provide a quick indication of carcinogenic response and severe toxicity problems. CFSAN officials added that the results of long-term studies usually supercede the results of mutagenicity studies.

CFSAN designated nine studies or analyses as crucial to its review of aspartame because they provided information to detect nearly all types of observable toxicity, including carcinogenic potential. Seven of these studies related to FDA's approval of aspartame in dry foods in 1974; two others would later be reviewed in conjunction with FDA's approval of aspartame in carbonated beverages in 1983 (see ch. 6). Table 2.3 lists the nine crucial studies.

[1]Designed to determine if a substance causes genetic changes.

Table 2.3: Aspartame Crucial Studies

Full title	Short title[a]
Dry foods approval:	
Two-Year Toxicity Study in the Rat	Two-Year Rat Study
Lifetime Toxicity Study in the Rat	Lifetime Rat Study
104-Week Toxicity Study in the Mouse	Two-Year Mouse Study
106-Week Oral Toxicity Study in the Dog	Long-Term Dog Study
Two Generation Reproduction Study in the Rat	Multigeneration Rat Study
A Supplemental Study of Dog Brains from the 106-Week Oral Toxicity Study	Supplemental Dog Analysis
A Supplemental Study of Rat Brains from Two Toxicity Studies	Supplemental Rat Analysis
Carbonated Beverage Approval:	
110-Week Toxicity Study in the Mouse	Mouse DKP[b] Study
115-Week Toxicity Study in the Rat	Rat DKP[b] Study

[a]The studies will be referred to by their short titles throughout this report.

[b]Diketopiperazine (DKP) is a manufacturing byproduct of aspartame and a breakdown product resulting from prolonged storage or increasing the temperature of products containing aspartame.

Our review indicated the seven crucial studies for dry foods met the submission requirements for food additives as shown in table 2.1. Two of these studies for dry foods are actually supplemental analyses of other crucial studies. For instance, the Supplemental Rat Analysis was a study designed to review and examine the results from the Two-Year Rat Study and the Lifetime Rat Study. Searle submitted the data from these two supplemental analyses before the 1974 approval; the reports for these analyses were not formally submitted to FDA until after this approval. In addition, the Two-Year Mouse Study was submitted after the 1974 approval; however, FDA did not begin requiring a lifetime study on a second rodent species until the mid-1970's.

An area of repeated controversy involves whether FDA ever considered the Waisman Monkey Study as crucial to the approval of aspartame in dry foods. Dr. Robert Waisman, a researcher at the University of Wisconsin Medical Center, began a 52-week study to determine whether aspartame had the same effects on monkeys as phenylalanine; e.g., seizures. He died before completing this study. Searle nonetheless submitted this study to FDA for review. CFSAN included the Waisman Monkey Study in a list of crucial studies even though this type of study was not required for food additives.

In a December 8, 1975, memo of meeting, CFSAN pointed out that while the study had been listed as crucial, it should not really be considered so

because of its deficiencies. Although CFSAN reviewers found some of the dosed animals had experienced seizures, reviewers commented that it would be difficult to appraise the possible significance of this finding. CFSAN did postulate that the seizures were due to the large amount of phenylalanine present in the aspartame fed to the monkeys. While documentation showed CFSAN did not consider the study's findings as crucial, review comments indicated the study lent support to the need for labeling aspartame-containing foods as not suitable for phenylketonurics (PKUs).[2]

CFSAN Reviewed Aspartame Studies for Safety

CFSAN's evaluation of Searle's studies centered on the review of scientific data pertaining to aspartame's safety, including its chemical structure, intended uses and stability, projected daily consumption, and toxicity studies.

In reviewing food additives for safety, CFSAN considers two key elements: the toxicity and the expected human consumption. Based on the evaluation of a petitioner's research studies, CFSAN determines the safe level for long-term consumption—the Acceptable Daily Intake.

In determining the Acceptable Daily Intake, CFSAN reviews animal studies to find a no-effect level. Since humans may react to a substance differently than animals, food additive regulations require FDA to use a 100-fold safety factor when applying animal experimentation results to humans. For example, if the "no adverse effect level" in animal studies was 2,000 milligrams per kilogram of body weight per day (mg/kg/day), the Acceptable Daily Intake for humans would be 20 mg/kg. When sufficient clinical studies are conducted, the 100-fold safety factor is not required.

CFSAN also determines an additive's Estimated Daily Intake, which provides the estimated amount of daily consumption per individual. If CFSAN determines the Estimated Daily Intake to be below or equal to the Acceptable Daily Intake, FDA can approve the additive's use.

CFSAN also uses animal studies to evaluate an additive's carcinogenic potential. As specified in the Delaney Clause of the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act, no additive

[2]A phenylketonuric is an individual who has difficulty in metabolizing phenylalanine. This inherited disorder can cause mental retardation. Children born with this deficiency can develop to adults of normal intelligence, provided their condition is recognized soon after birth and dietary treatment is started.

can be deemed safe if it is found to induce cancer. If any indication of carcinogenicity is found, FDA will not approve an additive's use.

CFSAN reviewed all the studies submitted as part of Searle's aspartame petition and expressed concern about a number of issues. In a September 24, 1973, letter to Searle, CFSAN suggested Searle's food additive petition be withdrawn unless certain issues could be promptly resolved. The issues included the following:

- The nitrosation[3] potential of DKP or aspartame.
- The adequacy of data to determine the significance of certain findings, such as brain tumors noted in some studies, including the Two-Year Rat Study, a crucial study.
- The adequacy of data to determine the long-term effect of DKP. CFSAN considered three short-term toxicological DKP feeding studies submitted by Searle to be of limited value in assessing DKP's long-term safety. While the short-term DKP studies could serve to support some limited use of aspartame, long-term DKP studies were needed to support aspartame's use in certain foods (e.g., carbonated beverages).

In response to CFSAN's letter, Searle provided the following:

- Data on the nitrosation of compounds similar to aspartame and DKP. According to CFSAN's Division of Toxicology, the study showed similar compounds were extremely unstable in water and would preclude nitrosation. CFSAN concluded nitrosation of aspartame or DKP was not a problem.
- The Lifetime Rat Study. Based on this submission, CFSAN concluded the brain tumors observed in the Two-Year Rat Study did not appear to be caused by aspartame.
- Information on the ongoing Rat DKP Study and the Mouse DKP Study. CFSAN decided the completion of these studies was not needed for the approval of aspartame for use in dry foods.

In addition, Searle submitted a number of clinical studies that were not required. Due to the expected broad use of aspartame, Searle, with CFSAN's acknowledgement, conducted clinical studies to show aspartame's effect on various human subpopulations. Clinical studies are not normally submitted for the evaluation of a food additive. However, FDA's Center for Drugs and Biologics requires clinical studies when

[3]A chemical reaction that may occur when certain chemicals combine to form nitrosamines, some of which are carcinogens.

it assesses a new drug's safety. Therefore, CFSAN decided to have that center review the studies.

After reviewing the clinical studies, the Center for Drugs and Biologics stated it did not have sufficient information to assess aspartame's safety. It requested additional information on the clinical studies and information on the animal studies, stating that aspartame should be reviewed under drug regulations. CFSAN objected, stating that (1) aspartame was clearly intended to be used as a food additive, not as a drug, and (2) it had already reviewed the animal studies submitted on aspartame. Therefore, a review by the Center for Drugs and Biologics was not necessary, CFSAN believed.

In November 1973, FDA's Office of General Counsel commented on the above issues and determined that the aspartame review should be handled under the food provisions of the Federal Food, Drug, and Cosmetic Act. They concluded CFSAN should assume full responsibility for the review of aspartame studies and stated the Center for Drugs and Biologics' review should be regarded as advisory.

Searle submitted additional information pertaining to the clinical studies, including more detailed protocols and data tabulations. With the additional information, CFSAN concluded the clinical studies showed aspartame caused no apparent significant problems in humans. In support of CFSAN's use of the studies, members of the PBOI and the Commissioner's panel told us that based on their review of Searle's clinical studies, they believed the studies could be used for evaluating aspartame's safety.

Restricted Use of Aspartame Approved

Based on CFSAN's review of 119 studies, the Commissioner on July 22, 1974, signed a regulation approving the use of aspartame as a sweetener in

- dry, free-flowing sugar substitutes for table use (not to include use in cooking) in package units not to exceed the sweetening equivalent of two teaspoonfuls of sugar;
- sugar substitute tablets for sweetening hot beverages, including coffee and tea;
- cold breakfast cereals;
- chewing gum; and
- dry bases for beverages, instant coffee and tea, gelatins, puddings, fillings, and dairy product analog (imitation whipped cream) toppings.

Aspartame was also approved for use as a flavor enhancer in chewing gum.

CFSAN established the Acceptable Daily Intake for aspartame at 20 mg/kg. For a 132-pound person, this would represent an intake of 1,200 milligrams (equivalent to 60 teaspoons of sugar) of aspartame per day.

FDA required the statement "PHENYLKETONURICS: CONTAINS PHENYLALANINE" on labels of food products containing aspartame, because PKUs must restrict their intake of phenylalanine. Also, because aspartame loses sweetness when heated, the regulation provided that when aspartame was used as a sugar substitute for table use, its label must instruct against use in cooking or baking.

CFSAN advised Searle that because it had not submitted chronic studies for evaluating the long-term effects of DKP, aspartame was not approved for products that could have an appreciable breakdown to DKP; e.g., carbonated beverages.

However, after aspartame was approved for use in dry foods, Searle submitted to FDA 49 additional studies, including the Mouse DKP Study and the Rat DKP Study, crucial for establishing aspartame's use in carbonated beverages (see ch. 6). CFSAN's Division of Toxicology evaluated two DKP studies and, in an April 16, 1975, memorandum, concluded the Mouse DKP Study generally did not show compound-related toxic or tumorigenic effects.

The Rat DKP Study showed a significant incidence of uterine polyps (a mass of tissue projecting from the normal surface level of the mucous membrane lining of the uterus) in rats fed at the two highest dose levels as compared to rats not fed DKP. Pathologists from FDA and the Armed Forces Institute of Pathology and consultants selected by Searle made independent pathological evaluations of the uterine polyp tissues. Each review team concluded the polyps were not "cancerous, precancerous or potentially cancerous."

Objections Filed Against Aspartame

Within 30 days after the publication of a food additive regulation, individuals may file objections specifying the provisions of the regulation that are objectionable and the reasons for the objections, and request a formal public hearing. If FDA determines there are reasonable grounds

for the objections, it must convene a public hearing and consider all evidence and relevant material supporting the objection. FDA may stay the regulation if it determines the objections warrant it.

After FDA's approval of aspartame, three objections were filed: one by the Quaker Oats Company, Barrington, Illinois; one by John W. Olney, M.D., Washington University School of Medicine, St. Louis, Missouri; and one by Mr. James Turner, currently representing Community Nutrition Institute, Washington, D.C.

The Quaker Oats Company did not request a hearing but objected to the requirement that cold breakfast cereal labels contain the statement "PHENYLKETONURICS: CONTAINS PHENYLALANINE." The company stated the amount of phenylalanine contributed by protein ingredients in such cereals is about three times that contributed by aspartame. They contended such a statement would be "unnecessary and redundant" and requested it be omitted from cold breakfast cereal labels.

In responding to the objection, FDA agreed with the company's estimate on the amount of phenylalanine contributed by common ingredients in cereal but noted that FDA had already considered such an exemption as part of the aspartame petition and found it unacceptable in the interest of safety. FDA therefore decided that the warning statement should remain.

To address the other objectors' concerns, FDA agreed to convene a public hearing and began negotiating with the objectors concerning the hearing (see ch. 4).

Conclusions

Based on the available criteria, we believe Searle met all prescribed petition submission requirements and gave CFSAN the required studies for the assessment of aspartame's safety in dry foods.

In addition, we found documentation indicating CFSAN reviewed all 168 aspartame studies even though some were not required to be submitted by Searle. The documentation further indicates that CFSAN addressed the internal safety concerns raised during its review and used results from Searle's submitted studies to establish a safe consumption level. We believe FDA followed the requirements in approving aspartame for use in dry foods. However, we did not evaluate the scientific issues raised or the adequacy of FDA's resolution of these issues.

FDA Concluded Problems Did Not Invalidate Studies' Results

In approving aspartame or other food additives for marketing before 1975, FDA relied on the integrity of the manufacturer to submit reliable safety data. This integrity was questioned while FDA prepared for the public hearing requested by the objectors to aspartame's approval. In July 1975, FDA's Commissioner established a task force to review certain Searle animal studies, including those relating to aspartame. Preliminary results of this investigation raised questions about the accuracy and reliability of the data that CFSAN evaluated to establish aspartame's safety. As a result, FDA prevented Searle from marketing aspartame and in 1976 decided to conduct a more detailed investigation of 15 aspartame studies.

An FDA team investigated 3 of the studies and UAREP investigated the other 12 to determine if Searle submitted accurate and reliable data to FDA. In addition, the FDA team and UAREP considered how well the studies were conducted in reaching overall conclusions on each study. Although problems were found with the studies, CFSAN concluded it could use the studies as a basis to establish aspartame's safety. We believe the UAREP and the FDA team's investigations and CFSAN's evaluation of the aspartame studies were responsive to the 1975 task force findings on the aspartame studies. However, we did not evaluate the scientific issues raised or the adequacy of FDA's resolution of these issues.

FDA Found Problems With Searle Studies

In 1974 and 1975, FDA investigators identified problems with animal studies for two Searle drugs already marketed. Following this discovery, the FDA Commissioner appointed a task force to investigate animal studies supporting seven Searle products, including aspartame. The task force identified problems with the studies. As a result of the task force findings, the Commissioner placed a stay on FDA's approval of aspartame, preventing Searle from marketing it, and the Department of Justice instituted grand jury proceedings against Searle based on the findings in the animal studies for one drug product.

FDA Established a Task Force to Review Searle's Studies

On July 23, 1975, FDA's Commissioner appointed a task force because FDA investigators found problems with Searle's laboratory practices and inaccurate reporting of tumor findings on two marketed drugs, Flagyl and Aldactone.[1] For example, certain types of tumors noted on raw data entries of Flagyl tumor studies were unaccountably changed. Also,

[1]Flagyl is used to treat infections. Aldactone is an antihypertension drug.

Searle had submitted to FDA an incomplete report on the number of tumors seen in animals who had been given Aldactone.

The Commissioner directed the task force, composed of FDA pharmacologists and investigators, to review Searle's practices in conducting animal experiments and to determine if Searle submitted false information to FDA. The task force was to recommend appropriate regulatory actions based upon its findings. The task force selected for review 25 animal studies that supported seven products: the food additive aspartame and six drugs, including Flagyl and Aldactone. The task force considered for selection any drugs or food additives on which Searle had performed animal studies since 1968. They gave higher priority to products to be used over a long period of time and to those with a potential to cause tumors. Since aspartame was a food additive, it had highest priority based on the large number of people expected to use it over a long period.

In selecting animal studies for investigation, the task force gave higher priority to long-term animal studies, because such studies were potential indicators of long-term health effects that were not necessarily monitorable in humans. Moreover, these studies involved more animals, more observations, more record keeping, and more personnel. The task force selected 11 aspartame studies for investigation; Searle performed 9 and contracted with Hazleton Laboratory and the University of Wisconsin for the other 2 (see app. II for a list of these 11 studies).

Task Force Identified Problems That Prevented Searle From Marketing Aspartame

The task force found that many of the problems with the aspartame animal studies, as well as the drug animal studies, resulted from of a lack of quality control. For example, Searle technicians did not keep accurate and consistent reports on the animals' condition. In addition, protocols (written plans for a scientific experiment) were not followed in carrying out the studies. According to the task force members, without adequate control of every step of a study, one could not assess the adequacy of the results.

Based on preliminary task force findings, in December 1975, the FDA Commissioner placed a stay on the July 1974 aspartame approval, preventing Searle from marketing this product. Also, CFSAN had the task force seal the supporting data relating to the aspartame studies at Searle and Hazleton Laboratories until it could determine what actions to take.

The task force concluded that its investigation had uncovered evidence that Searle's practices were in violation of the Federal Food, Drug, and Cosmetic Act. They said "the results were so serious in some studies as to make it difficult, if not impossible, to draw conclusions regarding the full toxic potential of the products from the data." (See app. III for the task force's findings and CFSAN's comments.)

The task force report issued in 1976 recommended that

- the Department of Justice institute grand jury proceedings against Searle,[2]
- FDA establish regulations outlining good laboratory practice,[3] and
- FDA centers determine whether to take administrative and/or regulatory actions on each of the Searle products investigated.

CFSAN Concluded Aspartame Studies Were Reliable

Based upon the task force findings, CFSAN decided to perform a more detailed investigation of 15 aspartame studies to determine their accuracy and reliability by comparing Searle's data with the data in reports submitted to CFSAN. However, CFSAN lacked sufficient resources to perform such a review and believed it should select a group of scientists, independent of FDA and Searle. FDA asked Searle to contract with UAREP, a group of university pathologists. However, an FDA team began reviewing 3 of the 15 Searle studies. Four months later, UAREP began reviewing the other 12 studies.

FDA Scientists and University Pathologists Selected to Review 15 Studies

Before the 1975 task force, FDA relied on the integrity of the manufacturer to submit reliable safety data in supporting petitions for food additives such as aspartame. However, as a result of the task force findings, the FDA Commissioner stated the integrity of the submitted data supporting FDA's original approval of aspartame was questionable. He recommended a review mechanism that, "operating independently of but funded by Searle or other private sources, would promptly undertake to validate pre-selected studies that comprised the basis for [the] original approval of aspartame."

[2]The information collected on the drug studies served as a basis for convening a grand jury investigation of Searle. Searle was not indicted.

[3]FDA issued good laboratory practice regulations on December 22, 1978, which set standards for conducting animal studies.

CFSAN agreed it needed a process to determine the accuracy and reliability of the data in the aspartame studies. This process, known as "authentication," was to determine whether Searle's supporting data from the studies matched its submitted reports to FDA. Authentication would not include reviewing the experimental design of the studies,[4] determining the safety of aspartame, or determining that CFSAN was justified in initially approving aspartame. CFSAN would make the final decision on those issues. Authentication would determine whether CFSAN was justified in using Searle's aspartame studies to support the safety of the compound. To authenticate the studies, FDA chose UAREP, a consortium of nine universities established in 1966.

FDA officials believed the job would be unmanageable if UAREP attempted to review every aspartame study. Therefore, CFSAN used the following criteria for selecting studies:

- Studies ordinarily required by CFSAN to determine safety.
- Studies that, if they had shown a toxic effect, would lead to a different conclusion on safety.
- Studies relating to issues raised by the objectors (see ch. 2).
- Studies selected at random.

By following these criteria, CFSAN selected the following 15 aspartame studies, including 5 of the 11 investigated by the 1975 task force:

- The nine crucial studies (see ch. 2).
- Three studies suggested by the objectors.
- Three random studies.

(See app. II for a list of the 15 studies.)

In April 1977, an FDA team began authenticating 3 of the 15 studies. Later, Searle entered into a contract with UAREP that was agreeable to FDA. This contract stipulated the authentication effort was to be an independent process with neither Searle nor FDA controlling or influencing the work, even though Searle was paying for it. In August 1977, UAREP began investigating the 12 remaining aspartame studies.

[4]Experimental design of the study is the plan for conducting the experiment and is usually written in the protocol that is formulated before the experiment is begun.

FDA Team Investigated Three Searle Studies

An FDA team investigated the Rat DKP Study (one of the crucial studies) and two teratology studies. The investigative team consisted of experienced field investigators supported by CFSAN scientists. In addition, a pathologist from FDA's National Center for Toxicological Research examined 7,872 slides and 7,360 tissue blocks from the Rat DKP Study.

The investigative team identified quality control problems in the three studies investigated. The team submitted its report to CFSAN officials, who concluded the differences between the original and submitted data were not of "such magnitude that they would significantly alter the conclusions of the studies." (See app. IV for a more complete list of problems and CFSAN's comments.) Some of the major problems identified and CFSAN's comments are discussed in the following paragraphs.

1. The investigative team found the diets in the Rat DKP Study may not have been homogeneous because no records existed on tests performed on the feed mixture's composition. Two reports indicated feed samples were not homogeneous. If the feed was not homogeneous, the rats could eat around the DKP and not consume it. Additionally, the team found a photograph of feed in a Searle analyst's notebook that clearly showed DKP particles distributed nonuniformly throughout the mixture.

CFSAN officials could not determine with any certainty that the diets were homogeneous. However, they believed there was evidence that the diets may have been homogeneous because of a dose-related increase in the incidence in uterine polyps and decrease in blood cholesterol levels.

2. In addition, the team found many of the tissues in the Rat DKP Study appeared to have been omitted due to autolysis (a breakdown of all or part of a tissue). The 1975 task force also found evidence of tissue loss from autolysis.

CFSAN officials found the tissue loss from autolysis was distributed among all dose groups and did not appear to occur selectively; e.g., mainly within a particular tissue or group. Hence, they could not determine whether the results would have been altered if these tissues had been obtained before autolysis.

3. According to the investigative team's report, the examination of fetuses and the reporting of the results in the two teratology studies were inadequate. For example, they found that 329 examinations were performed in 2 days—an impossible feat for one person. In addition, not enough tissue sections were taken through the heart.

CFSAN officials noted the Searle scientist who performed these examinations estimated that he examined about 30 fetuses a day, but CFSAN officials could not determine from the available data when these examinations were done. Additionally, instruction manuals were not specific on the number of tissue sections to be taken through the heart. CFSAN concluded

"... while there was no evidence that the study was compromised by this issue, the practice of not making enough tissue sections through the organs, as specified in the protocol, did not preclude a possible failure to observe abnormalities which may have occurred."

In September 1977, CFSAN reported its findings to the FDA Commissioner, who advised Searle that FDA's tentative acceptance of these three studies as authentic reflections of the data in Searle's possession did not constitute an endorsement of the adequacy of aspartame. The Commissioner indicated that the final determination of the scientific merit of these 3 studies, as well as the other 12, could only be made in conjunction with the evaluation of the UAREP report and that FDA would await the completion of the UAREP review before proceeding further.

UAREP Authenticated Remaining 12 Studies

In August 1977, after 8 months of contract discussion between FDA and Searle, UAREP began authenticating 12 studies. According to the UAREP report, it reviewed 2,200 pages of materials submitted by Searle to FDA on the 12 studies. In addition, Searle provided over 21,000 pages of background materials to UAREP. The UAREP pathologists diagnosed 39,000 tissue sections for 4,900 animals, including clinical observations, food consumption, weight changes, clinical laboratory tests, and autopsy results. FDA received UAREP's final report in 1978.

UAREP did not find evidence that animals in any one group had been treated deliberately to produce biased results. They concluded that the data submitted by Searle on the 12 studies were authentic. Although UAREP noted a "substantial number of minor and inconsequential discrepancies" in the studies, "there were few, if any discrepancies which would produce a change of greater than 5 percent in the final numerical data being compared."

One of UAREP's concerns during the authentication of Searle's aspartame studies was to be sure its efforts were free from Searle's influence or even the appearance of influence. Therefore, UAREP documented all communications between Searle and UAREP and eventually turned over these

documents to FDA. According to UAREP's principal investigator, UAREP only provided Searle

". . . with drafts of the general introduction, which included formulas for aspartame and how it was metabolized . . . Searle did not see a single word of the summary and conclusions until it received a copy of the final report." UAREP told Searle to relay its comments regarding the report to FDA.

At the request of CFSAN, FDA scientists reviewed UAREP's final report to determine whether any discrepancies noted by UAREP were sufficient to invalidate the studies' results. The FDA scientists agreed with UAREP that the data submitted by Searle were authentic. They also commented on the issues noted by UAREP. Some of these issues and the FDA scientists' comments are discussed in the following paragraphs.

1. UAREP noted that during the study, abnormal tissue masses were reported as present and then not observed at subsequent intervals. It believed when multiple pathologists examined tissues, some would miss abnormal tissue masses.

The FDA scientists stated that one would expect to find variations in diagnoses between trained pathologists.

2. Although UAREP noted some differences between its diagnoses and the original ones, UAREP did not believe the differences were significant. The UAREP pathologists reviewed these studies blind.[5] According to UAREP's president at the time of its review,

". . . the thing that impressed [UAREP] throughout the study, . . . which is reflected in our final statements and conclusions, was that the interpretation of the experimental results by previous observers did not really differ very significantly from ours following our review of the material."

The FDA scientists said the differences between UAREP's diagnoses and the original diagnoses were probably the result of different pathological interpretations. Additionally, one scientist said these differences did not represent an impressive list of discrepancies, considering the large number of microscopic sections involved.

[5]"Blind" means that the pathologist did not know if the tissue slides were from control or treated animals, and was unaware of previous diagnoses. UAREP's principal investigator compared the pathologists' diagnoses with Searle's original diagnoses.

Aspartame Studies Reviewed for Conduct

Searle conducted aspartame studies in the early 1970's, before the implementation of FDA's good laboratory practice regulations. The problems found with Searle's studies resulted in controversy over whether UAREP's and the investigative team's reviews considered how the studies were conducted and whether CFSAN was justified in using Searle's aspartame studies to support its safety.

An FDA scientist stated that a review of the studies' conduct can be done two ways. The first requires that someone be present when the study is conducted to determine exactly what occurs. This, of course, is the most accurate method, but was not practical. In fact, UAREP's principal investigator said it is impractical to have 24-hour surveillance of a study.

The second type of review assesses the conduct of the studies by reconstructing the studies from available supporting data. UAREP scientists and scientists on the investigative team informed us that they reconstructed the studies when they examined the aspartame data. According to UAREP's principal investigator, UAREP looked at the studies' conduct by assessing

- protocols and amendments;
- clinical observations;
- body weight, food, and compound consumption;
- clinical laboratory tests;
- ophthalmoscopic observations;
- necropsy (autopsy);
- survival data;
- histopathology (microscopic examination of the tissues);
- personnel, facilities, and methods;
- animals and animal care; and
- data production, handling, and storage.

For example, UAREP

- reviewed the protocol and amendments to determine whether the experiments were carried out according to the plans;
- examined tissue slides to determine the quality of the preparation of the slides and to verify the diagnoses of the lesions; and
- interviewed some present and former Searle personnel who worked on these studies. In addition, UAREP reviewed curriculum vitae for professional personnel at Searle and Hazleton.

UAREP officials also visited the laboratories that performed the aspartame studies. They noted these laboratories were accredited by the American Association for the Accreditation of Laboratory Animal Care[6] when the aspartame studies were conducted. According to UAREP's principal investigator, UAREP also considered the studies' conduct in reaching its conclusions. UAREP concluded that procedural problems were not of sufficient magnitude to invalidate the studies' conclusions. For example, if some animals' weights were missing, UAREP determined whether the missing weights made any difference in the study's final conclusions. UAREP found the missing weights were "not a major factor." In addition, according to a former president of UAREP, had UAREP "found something that would have affected the study, we would most certainly have reported it."

CFSAN believed that based upon the investigative team and UAREP authentication efforts, it was justified in using Searle studies in 1974 to support aspartame's safety. Based on the authentication efforts, FDA concluded it could hold a public hearing on the objections to aspartame's approval.

Conclusions

FDA investigators and scientists identified problems in a number of the crucial aspartame studies. Some believed the studies could not be used to determine aspartame's toxic potential. In response, FDA had an independent organization and an FDA team investigate the supporting studies for accuracy and reliability and concluded that the studies could be used to assess aspartame's safety. We believe that FDA's actions were appropriate and that UAREP and CFSAN addressed the conduct of the studies.

[6]This association inspected laboratories to determine whether they met certain standards for accreditation.

Public Board of Inquiry Revoked Aspartame's Approval

Shortly after FDA's 1974 approval of aspartame's use in dry foods, two objectors requested that FDA hold a public hearing concerning aspartame's safety. However, FDA delayed the hearing until it reviewed problems identified in the 1975 task force report (see ch. 3), and was assured certain Searle studies could be used to establish aspartame's safety.

Six years later, a PBOI, composed of three university scientists, heard testimony from the objectors and Searle and CFSAN officials concerning possible brain damage from aspartame's use and aspartame's ability to induce brain tumors. The PBOI concluded that aspartame would not increase the incidence of brain damage. However, it raised concerns over two of the three crucial studies used to discuss the brain tumor issue during the hearing. Therefore, the PBOI used its authority to revoke aspartame's approval and decided more studies were needed before Searle could market aspartame. The PBOI's decision would be binding unless overturned by FDA's Commissioner.

In addition, the PBOI denied the objectors' request to discuss the conduct of Searle's studies. The PBOI stated it could not undertake such an examination during the 3-day hearing and believed its purpose was to interpret the aspartame studies' data.

PBOI Selected to Address Issues on Aspartame's Safety

In August 1974, Dr. Olney and Mr. Turner objected to aspartame's approval and requested a hearing. After discussions with FDA, the objectors agreed to a PBOI, which would provide for a scientific evaluation of aspartame's safety. Therefore, they waived their right to a formal evidentiary hearing before an administrative law judge, which in 1975, had about a 6-month backlog. An adverse decision by the PBOI would have revoked aspartame's approval for use in dry foods unless FDA's Commissioner ruled otherwise.

The PBOI was delayed because both UAREP and the FDA investigative team did not complete their authentication reviews until 1978, and the PBOI issues were not agreed to by the objectors and FDA until 1979.

The final issues, as published in the Federal Register on June 1, 1979, follow:

1. Whether ingestion of aspartame, alone or together with glutamate,[1] poses a risk of contributing to mental retardation, brain damage, or undesirable effects on the neuroendocrine system.[2]

2. Whether ingestion of aspartame may induce brain tumors in the rat.

3. On the basis of answers to the above questions, should aspartame be allowed for use in foods or should approval be withdrawn? If allowed for use in foods, what conditions of use and labeling (if any) should be required?

The brain damage issue arose because Dr. Olney had performed studies showing that glutamate and/or aspartic acid caused brain damage in various species, including monkeys. He thought aspartic acid, when ingested alone or with glutamate, could result in brain lesions, abnormal development, and obesity. In addition, he suggested aspartame could cause mental retardation in PKUs.

The second issue, the brain tumor issue, surfaced as Dr. Olney prepared for the PBOI. While examining aspartame animal studies in FDA's files in 1978, Dr. Olney found 12 brain tumors in 320 dosed rats as contrasted to none in 120 control rats. Dr. Olney explained this many brain tumors in rats was rare, citing several references in support of his claim.

After CFSAN and the objectors agreed to the issues, each nominated five individuals to serve on the PBOI. Searle, as a participant, also nominated five individuals. From these lists of nominees, FDA's Acting Commissioner selected

- Walle Nauta, M.D., Ph.D. (Chairman), a neuroanatomist from Massachusetts Institute of Technology, from CFSAN's list;
- Peter Lampert, M.D., a clinical pathologist from the University of California at San Diego, from Dr. Olney and Mr. Turner's list; and
- Vernon Young, Ph.D., a nutritional biochemist from Massachusetts Institute of Technology, from Searle's list.

Beginning on January 30, 1980, the PBOI held a 3-day hearing during which the objectors, Searle, and CFSAN presented their evidence on the brain damage and brain tumor issues.

[1]An amino acid capable of producing a certain type of damage in some regions of the brain.

[2]Relates to the nervous system and the endocrine (hormonal) system.

PBOI Concluded Aspartame Would Not Increase Brain Damage

The PBOI members agreed with CFSAN and concluded that the ingestion of aspartame, either alone or together with glutamate, cannot be expected to increase the incidence of brain damage. The PBOI assessed aspartame's two component amino acids, aspartic acid and phenylalanine, because each was associated with a particular form of brain damage. Aspartic acid and glutamate, according to Dr. Olney, could cause lesions in certain brain regions and could also cause endocrine changes, resulting in growth and development problems. Phenylalanine was known to cause mental retardation in a small number of genetically susceptible individuals.

Searle's clinical studies did not produce significant toxic effects due to glutamate and aspartic acid when subjects consumed aspartame. Its studies also showed that the amount of phenylalanine resulting from aspartame ingestion under normal and abuse conditions would not significantly affect normal individuals or PKUs.

Aspartame's Aspartic Acid Content Below Toxic Level

The PBOI members agreed with Dr. Olney that aspartic acid and glutamate produced toxic effects, and that a significant proportion of ingested aspartic acid was converted to glutamate. Dr. Olney believed the ingestion of aspartame, either alone or together with glutamate, could increase

- the risk of brain damage by producing a certain type of lesion in some regions of the brain and
- the risk of endocrine problems in children, such as altered growth and development, which might not become evident until adulthood.

Dr. Olney based his objections on studies that administered doses of glutamate, aspartic acid, or aspartame to rodents and showed that when glutamate and aspartic acid are ingested together, "each agent augments the neurotoxic[3] effects of the other." He also presented a monkey study which showed that a "silent lesion" formed when glutamate was consumed. According to Dr. Olney, a "silent lesion" affects certain brain regions that control growth and development, but the effects are not noticeable until adolescence or adulthood. These effects could not be traced retrospectively to aspartame or to aspartame with glutamate. However, Searle's monkey studies showed no effects from ingesting large doses of aspartame.

[3]Poisonous or destructive to nerve tissue.

The PBOI decided that an inconceivably high intake of aspartame was required to reach toxic levels of glutamate and aspartic acid in the body. For example, aspartame studies presented during the hearing showed a single aspartame dose as high as 12,000 mg (equivalent to 600 teaspoons of sugar) for a 132-pound individual would not produce toxic effects. Studies also showed increased aspartic acid and glutamate levels were "short-lived, receding to a baseline in three hours." Therefore, repeat doses, when spaced 3 hours apart, were unlikely to increase the levels much beyond that induced by the first dose.

Searle had also conducted studies to determine the risk of aspartame ingestion in special population groups. These studies included

- the metabolism of aspartame by 1-year-old infants,
- the effect of aspartame on breast milk composition in lactating women, and
- the degree of placental transfer of aspartame in pregnant monkeys.

The PBOI members evaluated these studies at the hearing and agreed with CFSAN that infants, as well as adults, were protected against high surges of ingested aspartic acid, either alone or with glutamate, because of a biological mechanism in the body. According to the PBOI members, a dose of aspartame equivalent to ingestion of 150 aspartame tablets by lactating women showed no significant elevation of aspartic acid and glutamate, and did not increase the breast-fed infant's daily intake of aspartic acid and glutamate by more than 1 mg/kg. The members based their evaluation of the placental transfer of aspartic acid to the fetus on Searle's studies performed on pregnant monkeys. They found both the mother and the fetus were thoroughly protected against toxic aspartic acid levels.

Aspartame's Phenylalanine Content Not an Additional Risk

The objectors believed phenylalanine in aspartame could affect five categories of people:

- normal individuals;
- unidentified PKU children;
- pregnant PKU women, whose fetuses could be damaged when exposed to high levels of phenylalanine in the blood;
- individuals identified as PKUs, especially women; and
- PKU children who had gone off their diets.

After reviewing the objectors' concerns, the PBOI concluded the amount of phenylalanine resulting from aspartame's ingestion under normal and abuse conditions would not significantly affect these categories of individuals. They also believed the labeling required by FDA in 1974, when it originally approved aspartame, would be adequate to protect PKUs. For each of these categories, we summarize the objectors' concerns and the PBOI evaluation of those concerns in the following sections.

Normal Individuals

Objectors' Concerns

Claimed the 34 mg/kg/day consumption level set by the PBOI as the benchmark for analyzing the safety of aspartame was too low. Said the amount of phenylalanine ingested in aspartame may have different implications than the phenylalanine in protein.

PBOI Conclusions

The PBOI adopted the 34 mg/kg/day of aspartame as the level to assess the risk of aspartame. It said 34 mg/kg/day of aspartame only caused the phenylalanine levels to rise to that level normally found in adults and children following a protein-rich meal. Therefore, the PBOI believed that the phenylalanine from aspartame did not present a risk to normal individuals.

Unidentified PKU Children

Objectors' Concern

They said 30 percent of all PKU children in the United States may not be diagnosed. Therefore, marketing aspartame in foods that predictably will be heavily consumed by unidentified PKU children was not justified.

PBOI Conclusions

Based on a consultant's testimony at the PBOI, 10 percent of the 200 PKU children born annually in the United States remain undiagnosed. These undiagnosed children would first be adversely affected by the normal amount of phenylalanine provided in breast milk protein or infant formula. Therefore, these children were at risk first and foremost by being undiagnosed and permitted to consume meals that were standard for normal children. The argument that aspartame in the food supply

would significantly increase the risk of mental retardation in these children was not supported.

Pregnant PKU Women

Objectors' Concerns

They believed the fetus could be damaged if exposed to high levels of phenylalanine consumed by the mother. They wanted to have a label warning against aspartame's use during pregnancy and breast feeding.

PBOI Conclusions

It said the ingestion of 34 mg/kg/day of aspartame would have the phenylalanine equivalent of a "little more than two extra glasses of milk." It believed these women were at a much higher risk from the consumption of natural foods than from aspartame's use.

Individuals Identified as PKU, Especially Women

Objectors' Concerns

They believed aspartame would contribute to the severity of brain damage in some fetuses, and in others aspartame may make the difference between a normal or brain-damaged fetus.

PBOI Conclusions

It determined that these women would follow a carefully prescribed diet, and so a cautionary label that clearly identified aspartame as a source of phenylalanine would prevent liberal use of aspartame by these women.

PKU Children Who Go Off Their Diets

Objectors' Concerns

They believed the availability of aspartame in the food supply may cause these children to increase their phenylalanine considerably so that it is above the safe threshold level.

PBOI Conclusions

It compared the amounts of phenylalanine these children could consume through the usual food sources with the phenylalanine consumed in aspartame. It concluded the significant risk to these children was "clearly from the phenylalanine in the protein furnished by standard foods."

PBOI Concluded Further Studies Needed on Brain Tumors

The PBOI members based their decision regarding the brain tumor issue on the following three crucial studies:

- Lifetime Rat Study—A 2-year toxicity study to evaluate the effects of feeding aspartame at two dosage levels. These rats were the offspring of rats who had been fed aspartame.
- Two-Year Rat Study—A 2-year toxicity study to evaluate aspartame at four dosage levels.
- Rat DKP Study—A 2-year toxicity study to evaluate the effects of feeding DKP at three dosage levels.

The PBOI concluded the evidence from the Lifetime Rat Study and the Two-Year Rat Study

> ". . . do not rule out an oncogenic[4] effect of aspartame, and that, to the contrary, they appear to suggest the possibility that aspartame, at least when administered in the huge quantities employed in the studies, may contribute to the development of brain tumors."

The PBOI members concluded the Rat DKP Study showed no evidence of a carcinogenic effect.

Regarding the Lifetime Rat Study, Dr. Olney argued the spontaneous rate[5] of tumors found in control animals was too high. Dr. Olney cited evidence from scientific literature that showed only 49 tumors were found in 59,812 control rats, less than a 0.1-percent spontaneous rate. Therefore, he said the 3.5-percent rate found in the control rats in Searle's Lifetime Rat Study was very high. However, CFSAN said studies published in the scientific literature showed a "wide variation (from 0.09 to 5.8 percent) in the spontaneous rate for brain tumors in rats," and the control animals' rate in the Lifetime Rat Study was within this range. It also pointed out methodological problems in some of the studies

[4]Giving rise to tumors or tumor formation.

[5]The frequency of naturally occurring brain tumors found in rats not exposed to any test compound such as aspartame. It is compared to the frequency of brain tumors found in the dosed animals to determine whether the compound has an effect on the frequency of brain tumors.

cited by Dr. Olney. These problems might affect the spontaneous rate. For example, in one of the studies, the researchers did not use a microscope to examine organs unless they noted an abnormality in the organ. This could reduce the number of tumors found. Therefore, CFSAN concluded that the control animals in Searle's Lifetime Rat Study and Two-Year Rat Study were the most appropriate indicators of the spontaneous rate.

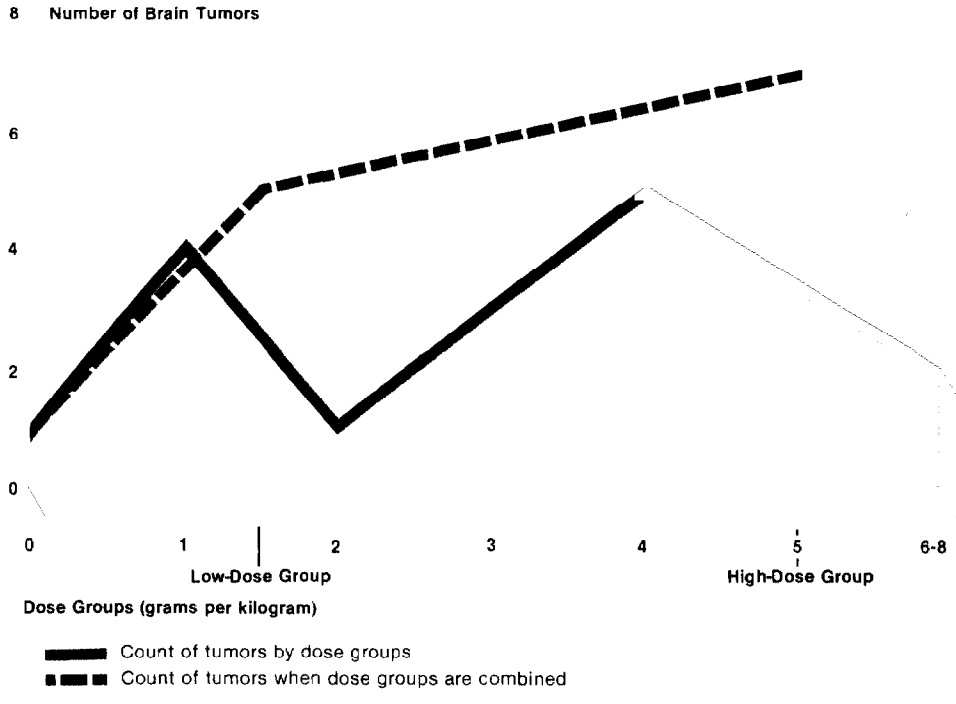
The PBOI members agreed with Dr. Olney that the Lifetime Rat Study should be discounted because of the high number of tumors in the control animals. The PBOI members thought the 3.5-percent rate was "bizarre when compared with the rate reported from [other studies on this strain of rat]."

In Searle's Two-Year Rat Study, Dr. Olney said the 320 aspartame-fed rats developed 6 brain tumors (1.88 percent) when they were less than 1-1/2 years old. Comparing this rate to the 0.1-percent spontaneous rate in other studies, Dr. Olney stated

> ". . . this was a very high incidence [rate and] . . . in a 1 and one-half year context it [was] an incredible and unprecedented occurrence which cannot be explained in terms of natural expectation."

The PBOI members believed the Two-Year Rat Study suggested a possible dose-effect relationship. In total, 13 brain tumors were diagnosed in the study—1 in the control group; 4 in the low dose group; 1 and 5, respectively, in the next 2 dose groups; and 2 in the high dose group. The PBOI combined the two lowest and the two highest dosed groups together, making the respective incidence rates 3.1 percent (5 tumors) and 4.3 percent (7 tumors), suggesting a possible dose-effect relationship (see figure 4.1 for PBOI's comparison). CFSAN and Searle did not believe a dose-effect relationship existed. A dose-effect relationship is one indication of carcinogenicity.

Figure 4.1: Comparison of Brain Tumors Among Dose Groups in the Two-Year Rat Study



Also, in assessing the dose-effect relationship in the Two-Year Rat Study, the PBOI believed a medulloblastoma[6] that occurred in the highest dose group could have been caused by aspartame. CFSAN concluded the medulloblastoma was probably not aspartame related because for the rat to have died from the medulloblastoma at 12 weeks of age, the tumor must have originated in embryonic tissue. In the Two-Year Rat Study, aspartame was not fed until 4 weeks after birth. CFSAN also noted that since the animal died after being given aspartame for 8 weeks, the amount of aspartame fed to that rat was small compared to the total received by all other rats in the dosed groups. CFSAN believed the Life-time Rat Study (a study of fetuses exposed to aspartame) supported its arguments because no medulloblastomas occurred in any of the fetuses.

Another indication that a compound has carcinogenic potential is the early occurrence of tumors in dosed animals. The PBOI members reported that two aspartame-fed rats in the Two-Year Rat Study died at an early age from tumors. One rat died at 8 weeks and another at 16 weeks,

[6]A brain tumor that usually occurs in embryonic tissue.

thereby reinforcing the PBOI members' belief that aspartame could be a tumor-causing compound. As a result of the findings from the Two-Year Rat Study and the Lifetime Rat Study, the PBOI concluded in October 1980 that Searle's aspartame studies did not provide sufficient evidence to prove aspartame's safety. Therefore, it revoked the regulation approving aspartame and suggested that further studies be performed to determine the carcinogenic potential of aspartame before it was allowed on the market. Since the PBOI decided against aspartame's approval, it did not address the labeling issue in its conclusions.

PBOI Did Not Address Studies' Conduct or Carbonated Beverages

During the 3-day hearing, the objectors asked the PBOI members to examine how well Searle's studies were conducted. A photograph from the Rat DKP Study was shown to the PBOI as evidence of problems in the conduct of Searle's aspartame studies. This photograph, which showed animal feed with large chunks of DKP, provided evidence that the animals in the study might not have eaten the DKP. However, the PBOI refused this request, stating it could not undertake "a retrospective quality inspection" of all the studies submitted as evidence at the hearing.

About 1 month later and before the PBOI's decision, Mr. Turner asked the PBOI to reconsider its decision and to reconvene to consider evidence on how well the studies were conducted. He also appealed to FDA's Commissioner, arguing that the PBOI was required to make such an examination as part of its responsibility to determine the safety of aspartame. Mr. Turner believed he had the right to discuss this issue at the PBOI because of a letter from the Department of Health and Human Services' general counsel. In addition, a letter from an FDA official stated that questions relating to the brain damage and brain tumor issues could be discussed based upon available evidence. Mr. Turner interpreted this to mean that Searle's conduct of the studies could be discussed at the PBOI hearing.

The PBOI members disagreed with Mr. Turner's argument since CAREP and CFSAN considered and resolved, before the PBOI hearing, questions about the studies' conduct. In addition, the members believed the evidence presented by Mr. Turner was outside the scope of the PBOI issues. They believed their charge involved interpreting the data and not analyzing the studies' conduct. Furthermore, the PBOI members concluded since FDA's Commissioner had not asked them to consider the types of questions raised by Mr. Turner, they found it unnecessary to hold another hearing to consider this evidence.

Another controversy involved whether the PBOI should have considered carbonated beverages in its decision. The Federal Food, Drug, and Cosmetic Act requires that objections at a public hearing relate to either the approval or disapproval of a food additive petition. The objections raised before the PBOI related only to FDA's approval of a petition for aspartame's use in dry foods. At the time of the PBOI, aspartame's use in carbonated beverages was not at issue since a petition for such use had not been approved or disapproved. A representative of the department's general counsel assigned to advise the PBOI members told us it would have been "legally impermissible" for the PBOI to reach a decision based on "anything involved with carbonated beverages."

Conclusions

We believe FDA followed the required process by holding a PBOI, which gave the objectors a scientific inquiry on their safety concerns regarding aspartame. Furthermore, we believe the PBOI addressed all the issues as agreed to by CFSAN and the objectors.

Based on the evidence presented at the hearing, the PBOI concluded aspartame did not cause brain damage at the estimated consumption levels. However, it revoked the aspartame regulation because it believed additional studies were needed to show that aspartame does not cause brain tumors.

The PBOI used its authority to refuse Mr. Turner's request for a retrospective quality review of Searle's studies because it believed CFSAN and UAREP had already resolved those questions. In fact, FDA delayed the PBOI pending such assurances.

We believe the PBOI was also correct in not considering carbonated beverages in its decision. Aspartame's use in such beverages was not approved or disapproved at the time of the PBOI. Consequently, aspartame's use in carbonated beverages was not at issue.

FDA Reapproved Aspartame in Dry Foods

After the PBOI's decision not to approve aspartame in dry foods, the hearing participants filed rebuttals. The objectors continued to believe that aspartame may cause brain damage and additional animal studies were needed. CFSAN and Searle argued the studies showed aspartame did not cause brain tumors. The FDA Commissioner had to decide whether to agree with the PBOI or overturn its decision and allow aspartame to be marketed in dry foods.

A panel of FDA scientists and a Department of Health and Human Services lawyer reviewed the PBOI decision and the hearing participants' rebuttals, and provided advice to the FDA Commissioner on the issues. The Commissioner's panel was unable to reach a consensus on the issues. It agreed with the PBOI's decision that at the projected levels of consumption, aspartame would not cause brain damage. However, three of the five panel members did not believe Searle's studies conclusively showed that aspartame did not cause brain tumors.

After being briefed by the panel members and reviewing the information on the various issues, the Commissioner, on July 18, 1981, approved aspartame's use in dry foods. The Commissioner said that he received no pressure to approve aspartame, his decision was intellectually honest, and he was persuaded by the data that aspartame should be approved.

Panel Formed to Advise Commissioner

FDA officials told us that after a public hearing, such as the one held on aspartame, a panel reviews the decision and the issues discussed at the hearing, and summarizes for the Commissioner both sides of the issues. If the evidence clearly supports a decision for or against approval, the panel may recommend one decision to the Commissioner over the other.

According to FDA regulations (21 C.F.R. 10.55), panel members and the Commissioner were not permitted to have private discussions about the PBOI aspartame decision with CFSAN officials or anyone involved in the PBOI. Also, CFSAN officials were not permitted to serve on the Commissioner's panel.

The panel usually consists of a department lawyer and a representative from FDA's Office of Health Affairs. FDA officials involved with the Commissioner's panel told us the panel on aspartame consisted of more members than most panels because of the complexity of the issues. The aspartame panel consisted of a lawyer, two biochemists (from the Office of Health Affairs and FDA's National Center for Toxicological Research), two statisticians (from FDA's Center for Veterinary Medicine and Center

for Drugs and Biologics), two pathologists (from the Center for Drugs and Biologics and the National Center for Toxicological Research), and a carcinogenicity specialist (from the National Center for Toxicological Research). The pathologist from the Center for Drugs and Biologics and the biochemist from the National Center for Toxicological Research reviewed the brain damage issue, while the remaining panel members reviewed the brain tumor issue. The lawyer headed the Commissioner's panel and drafted the Commissioner's final decision.

On the day of the PBOI decision, Searle filed suit attempting to prevent the FDA Commissioner from delaying his decision. However, Searle agreed it would not press the lawsuit until June 1, 1981. Therefore, the panel worked to meet the deadline.

Commissioner Agreed Aspartame Does Not Increase Brain Damage

The major objections to the PBOI's decision on the brain damage issue came from Dr. Olney. In his rebuttal to the PBOI's decision, Dr. Olney argued that Searle had not shown aspartame does not cause brain damage. Dr. Olney believed that additional studies were needed to show the combined effect of aspartame and glutamate on children and that aspartame posed a risk to undiagnosed PKU fetuses.

In his rebuttal, Dr. Olney said his most serious exception pertained to the PBOI's decision that the risk of brain damage to humans when ingesting aspartame either alone or with glutamate was negligible. His main objection was that none of the studies was designed to determine whether the glutamate and aspartic acid levels might rise above the toxic threshold in children consuming aspartame and glutamate together. Therefore, Dr. Olney said the PBOI should revise its decision to recommend additional studies in children.

The panel member reviewing this issue said he agreed with the PBOI's conclusion. Although no study was done on children's consumption of glutamate and aspartame together, separate studies on children's consumption of aspartame, glutamate, and aspartic acid showed children handled these compounds as well as adults. In addition, Searle conducted studies on adults that showed their blood levels when ingesting both aspartame and glutamate did not increase to toxic levels. Together these studies supported the PBOI's conclusion that, at the projected consumption levels, aspartame would not cause brain damage in adults or children. The Commissioner, in his decision, agreed with the PBOI's decision for the same reasons cited by the panel.

Dr. Olney raised two main exceptions with the PBOI's decision that PKU children were at little risk from aspartame. His first exception related to the percentage of PKU children not diagnosed at birth. He stated the PBOI was incorrect to say 10 percent of PKU children in this country remain undiagnosed and claimed that a more realistic estimate was 30 percent.

The panel member reviewing this issue and relying on experts' testimony during the hearing found no basis for disagreeing with the PBOI's decision. The Commissioner acknowledged the number of undiagnosed children at birth was subject to dispute. However, the Commissioner said he relied on "a consultant to the [PBOI] and an acknowledged expert on PKU" who emphasized that even a PKU infant needs 90 mg/kg/day of phenylalanine as an essential nutrient. Since aspartame was not approved for infant formulas or foods, the undiagnosed PKU infants would not be at any additional risk from aspartame. This expert also stated that nearly all PKU children who are not diagnosed at birth are diagnosed by 8 to 10 months of age.

Dr. Olney's second exception related to pregnant women who are unaware they are PKUs. He said these women may use aspartame heavily during pregnancy, which could lead to mental retardation of a fetus. He stated although this may affect only a few cases each year, he believed it should be prevented by not approving aspartame.

The panel member reviewing this issue agreed with Dr. Olney that aspartame may cause a few cases of mental retardation a year and suggested labeling of aspartame products, advising pregnant women to consult their physician. However, in his decision, the Commissioner stated "this problem exists whether or not aspartame is marketed." He said he agreed with the PBOI's conclusion that the phenylalanine from normal food posed "a much greater risk" than aspartame, and he stated the "only remedy to this problem . . . is first to identify the women who have this condition and then put them on a phenylalanine restricted diet." Therefore, the Commissioner concluded that additional labeling for pregnant women was not needed (see ch. 4).

Panel Did Not Reach a Consensus on the Brain Tumor Issue

CFSAN and Searle claimed that because of several errors in the PBOI's analyses of Searle's Two-Year Rat Study and Lifetime Rat Study, the PBOI concluded the studies did not support aspartame's safety. The Commissioner's panel agreed that the PBOI made some errors in its analyses of the data. Also, some panel members raised new issues not discussed at the PBOI and concluded that aspartame's safety was not shown. Three

of the five panel members reviewing the brain tumor issue did not believe Searle's studies conclusively showed that aspartame did not cause brain tumors.

CFSAN Identified Errors in the PBOI's Analyses

In their rebuttals, Searle and CFSAN argued the PBOI should not have discounted the Lifetime Rat Study as "bizarre" because of the high spontaneous rate of tumors in its control group. In addition, they said the PBOI's analyses of the Two-Year Rat Study were in error because the PBOI

- unscientifically combined dose groups,
- erred on the age of two rats that died, and
- included a medulloblastoma in its analysis.

CFSAN and Searle claimed that according to their analyses, the Two-Year Rat Study showed aspartame does not cause brain tumors.

The most controversial issue in the Lifetime Rat Study was whether the spontaneous rate of brain tumors for control animals in this study differed significantly from the rates reported in the scientific literature (historical rates). CFSAN disagreed with the PBOI's conclusion to discount the Lifetime Rat Study because of its high tumor rate (3.5 percent) in the control animals. CFSAN argued the historical studies cited by the PBOI with a low spontaneous rate of brain tumors had methodological problems (see ch. 4). In addition, they said because Searle's studies examined more brain sections than the studies cited by the PBOI, one would expect to find more tumors in both control and dose groups than studies examining fewer brain sections. CFSAN also cited a National Cancer Institute study reporting a 2.2-percent spontaneous rate and an article describing three studies not discussed at the PBOI which concluded that the spontaneous rate was 2.1 to 3.3 percent.

The panel's documents show panel members also disagreed on the spontaneous rate issue. Two panel members concluded that the spontaneous rate ranged from 1 to 3 percent and, therefore, the tumor rate (3.5 percent) in the Lifetime Rat Study control group was not unexpected. They concluded that it was more appropriate to use the spontaneous rate for a study's control animals than rates from other studies because the animals within a study are most similar. For example, animals within a study are usually obtained from the same breeder.

Two other panel members agreed it was more appropriate to use the spontaneous rate associated with the control animals in Searle's studies

than historical rates. However, they agreed with the PBOI that the high spontaneous rate in the Lifetime Rat Study cast some doubt on that study's quality. They said Searle should have done another study to confirm that the spontaneous rate was correct and that the study was well conducted.

In his decision, the Commissioner agreed with CFSAN and the two panel members that the spontaneous rates in Searle's studies were consistent with the historical rates. He said the studies relied on by the PBOI were flawed and other credible studies reported spontaneous rates in the mid-1-percent and 2-percent range. In addition, he said the studies with fewer animals (comparable to the Lifetime Rat Study) reported spontaneous rates in the 3-percent range or higher. Comparing the rate of brain tumors in the control animals in Searle's Lifetime Rat Study with the rates in its dose groups showed no dose effect. Therefore, the Commissioner accepted the Lifetime Rat Study as showing aspartame does not cause brain tumors.

Concerning the Two-Year Rat Study, CFSAN said the PBOI's combination of the two lowest and two highest dose groups (see figure 4.1), which showed a dose effect relationship, was scientifically unsound. CFSAN indicated "[u]nless adequate justification is provided, it is a fundamental scientific principle that one must analyze the data as the study was originally designed." One of the reasons for this is as more analyses are done, the chances of the data showing a false dose effect increase dramatically. The panel members agreed the PBOI should not have combined the dose groups in this manner, and in his decision, the Commissioner said the statistical tests done by CFSAN were more appropriate for analyzing the data than the PBOI's method.

In addition, CFSAN said it had rechecked the data on Searle's Two-Year Rat Study and found no mention of an animal dying at either 8 or 16 weeks of age as stated in the PBOI decision. This early occurrence of tumors supported the PBOI's decision that aspartame could be a tumor-causing compound. The panel reviewed the data and concluded that the PBOI erred. The data showed that the animals actually died at about the 69th week and the 76th week. As a result, the Commissioner concluded this study had no significant findings of early tumor onset.

CFSAN, using the same arguments as discussed in chapter 4, disagreed with the PBOI's conclusion that the medulloblastoma should be included in the Two-Year Rat Study's analyses. All the panel members who reviewed the brain tumor issue agreed that the medulloblastoma should

have been counted in the statistical analyses of the brain tumors because tumors cannot be arbitrarily omitted. However, two panel members said after statistical analyses were done, the inclusion of the medulloblastoma should be reviewed in the context of the rest of the data. They stated it was unlikely aspartame caused this tumor for the reasons cited by CFSAN (see ch. 4), and if this tumor was eliminated from the statistical analyses, the analyses would not show a dose response. The Lifetime Rat Study, which did not show evidence of aspartame causing tumors, confirmed this.

The Commissioner agreed the medulloblastoma should not be included in the analyses. Therefore, he concluded the Two-Year Rat Study did not show a dose response.

Panel Identified Additional Concerns

Before the Commissioner's decision, panel members identified concerns on which they could not reach a consensus. These concerns included whether

- the studies included enough animals to detect a significant increase in brain tumors,
- additional statistical tests showing statistically significant findings change the study's conclusions, and
- the studies' conduct was good enough to use the studies' results.

Issue papers prepared by the statisticians in 1981 showed Searle's studies did not support a decision on aspartame because they did not include enough animals to have a reasonable chance of detecting a 5-percent increase in tumor rate caused by aspartame. They claimed the Searle studies had a 90-percent probability of detecting a 20-percent increase in tumor rate[1] but only a 27.9-percent chance of detecting a 5-percent increase. Since a 5-percent increase in brain tumors in humans would be significant, a study should have a high probability of detecting this increase.

In 1986, the panel's carcinogenicity specialist and the pathologist advised us that Searle's studies contained only slightly fewer animals than is required by CFSAN today. Currently, CFSAN requires 50 animals for each sex in the dose and control groups. One panel member said the National Cancer Institute and the National Toxicology Program also require only 50 animals in each sex per group. For example, the

[1]The statistics cited in this section assume a confidence level of 95 percent.

Two-Year Rat Study had 40 animals per sex in each dose group and 60 animals per sex in the control group. To have a 90-percent probability of detecting a 5-percent increase in tumor rate, a study would need 320 animals per sex in each dose group. The biochemist added that even today, studies are not normally done with large numbers of animals because of cost and the difficulty of managing and controlling the study.

The carcinogenicity specialist told us to compensate for the small number of animals in the studies, the dosage given to the animals was exaggerated. For instance, in the Two-Year Rat Study, one dosage group was fed 6 to 8 grams of aspartame per day, which was 300-400 times the Acceptable Daily Intake set by FDA for humans at that time. The carcinogenicity specialist and pathologist believed this increased dose level compensated for the small number of animals.

Another concern of one statistician, as noted in a 1981 memorandum, was the significant findings identified by statistical tests. This statistician performed additional statistical tests on the results of the Two-Year Rat Study. He stated these additional significant findings showed aspartame could cause brain tumors.

The pathologist advised us that statistically significant findings in studies are not unusual. The more statistical tests done, the higher the chances of obtaining a significant finding. Such findings do not necessarily indicate a dose effect. The carcinogenicity specialist said the evaluation of a study does not rest solely on statistics. If statistics were the determining factor, other scientists would not be needed, because statisticians could determine whether the study showed carcinogenicity. A scientist must evaluate significant findings in the context of all data in that study as well as other studies.

After reading the UAREP report in 1981, three panel members were concerned about the conduct of Searle's studies. Their concerns related to the problems identified in UAREP's report, such as missing slides. The other two members indicated that they did not have enough information to reevaluate conduct. One of the two members also told us that no study is perfect and that he believed UAREP had addressed the conduct of Searle's studies.

Commissioner Approved Aspartame

The panel briefed the Commissioner twice and gave him information on the arguments for and against approval. The panel members who questioned aspartame's safety told us their concerns were adequately explained to the Commissioner.

In May 1986, the former Commissioner told us that after looking at the data, talking to the members of the panel, and doing some reading on his own, he believed the evidence supported aspartame's approval. He said he thought the decision was an honest one and the best he could make scientifically. He believed he had to make a decision because "if [you] wait for unanimity . . . nothing is ever going to happen."

Therefore, on July 18, 1981, the Commissioner signed the decision approving aspartame in dry foods. As part of the approval, FDA required Searle to monitor the consumption of aspartame and provide this information to FDA (see ch. 7). FDA believed the safety assessment on the brain damage issue was closely tied to the projected consumption levels.

In his decision, the Commissioner also agreed with the PBOI and denied Mr. Turner's appeal for a new hearing on the studies' conduct and a new review of the studies. He concluded a new hearing was not needed because Mr. Turner did not specifically state any deficiencies serious enough to warrant a hearing. According to the Commissioner, the only specific allegation cited by Mr. Turner or Dr. Olney was the homogeneity of the food in the Rat DKP Study. Their support was a photograph taken of food used for stability testing but not fed to the rats. The Commissioner believed that the evidence was not sufficient to invalidate this study.

In addition, because UAREP addressed conduct issues (see ch. 3), the Commissioner believed Mr. Turner's request for a new review of the studies was not warranted. Therefore, he denied Mr. Turner's appeal.

Controversies Surrounding the Commissioner's Decision

In his decision, the Commissioner cited a study done by a Japanese firm as additional support that aspartame did not cause brain tumors. This study was not available to the PBOI before its decision, and this study's use has been questioned. Searle submitted the Japanese study to FDA in its rebuttal to the PBOI decision. The panel members said although they looked at the study, they did not give it a detailed review and it was not used in their evaluation of the issues.

According to the department lawyer on the panel, the Commissioner could not use the Japanese study as support for aspartame's approval. In his decision, the Commissioner stated he had sufficient evidence to make a final decision and the Japanese study merely provided additional support for his conclusion.

Questions have been raised as to whether the panel or the Commissioner received pressure to approve aspartame. The panel members told us although they felt pressure to expedite their review because of Searle's lawsuit, they felt no pressure to recommend approval or disapproval of aspartame. The Commissioner also said he did not receive any pressure to approve or disapprove aspartame.

The FDA Commissioner independently approves food additive regulations. We found no evidence in FDA's files that anyone other than FDA or the Commissioner's panel was involved in the aspartame decision. Memoranda in FDA's files indicate that a department lawyer advised the Commissioner not to discuss his decision with the Secretary of Health and Human Services until it was final. Although he informed the Secretary of the decision's status, the former Commissioner advised us that he did not inform the Secretary of his decision until he had signed the regulation.

Current Opinions on Aspartame's Approval

When we talked in 1986 to the two members of the PBOI, the Commissioner's panel, and the former Commissioner about aspartame's approval, most of them said they had not changed their position on aspartame's approval. The PBOI chairman said although he still disagrees with some of the Commissioner's reasoning (i.e., the discounting of the medulloblastoma), "nothing seems to argue in favor of withdrawal of approval." He said he believes that neither aspartame nor DKP is a carcinogen and agrees that the PBOI did make an error on the time the two rats died in the Two-Year Rat Study. However, he believes the PBOI made the right decision because although "it is unlikely that the tumor issue is really a high risk one . . . it would have been more comforting if there had been a little more irrefutable proof." The other PBOI member said his reaction to the Commissioner's decision was a positive one. He thought Searle's rebuttal adequately answered the PBOI's questions.

The panel members still have differing views. Most of the panel members said they have not seen anything to change their minds on the aspartame issues. The two panel members who reviewed the brain damage issue agreed with the Commissioner's decision. One said she has

gained more knowledge on how the consumption of food additives is estimated. Therefore, she feels more comfortable with the decision, although she still thinks pregnant women and young children should limit their intake of aspartame. The two panel members reviewing the brain tumor issue and favoring approval still agree with the Commissioner's decision. Of the three panel members expressing concerns about aspartame's safety, two said they would not have approved aspartame because the evidence neither demonstrated aspartame's safety nor showed it to be unsafe. The third panel member said that if he had been the Commissioner, he probably would have approved aspartame.

The former Commissioner said he has seen nothing to change his mind on his decision. He said scientific judgments are questioned continuously.

CFSAN only recently saw the concerns raised by the panel members, because of FDA regulations regarding private discussion about PBOI decisions. After reviewing the panel members' concerns, CFSAN still believes Searle's studies supported aspartame's safety.

Conclusions

The FDA Commissioner had to consider a number of factors in deciding whether aspartame was safe. CFSAN and Searle believed the evidence supported aspartame's safety. The PBOI concluded, pending the completion of additional studies, that aspartame should not be marketed. The Commissioner's advisory panel could not reach a consensus on the brain tumor issue. The standard for approving aspartame did not require absolute safety but rather proof of reasonable certainty no harm would result from aspartame's use.

We believe the Commissioner was aware of the issues raised by the PBOI and the concerns of the panel members. We believe the necessary steps were taken to advise the Commissioner of the arguments for and against aspartame's approval. We did not find any evidence that pressure was put on the Commissioner to approve aspartame.

We also believe the Commissioner's final decision spelled out his basis for concluding that aspartame was safe.

FDA Approved Additional Uses of Aspartame

About a year after FDA reapproved aspartame's use in dry foods, Searle filed a petition proposing its use in carbonated beverages. CFSAN required Searle to submit additional information showing the safety of increased aspartame consumption and the extent of its breakdown in liquids. After reviewing Searle's submissions, FDA approved aspartame's use in carbonated beverages.

FDA also evaluated and approved aspartame's use in multivitamins, fruit juice and fruit-flavored drinks, frozen stick-type confections, breath mints, and tea beverages. We believe FDA followed the requirements (see chs. 1 and 2) in approving these additional uses.

FDA Approved Aspartame's Use in Carbonated Beverages

On September 8, 1982, Searle filed a petition proposing aspartame's use as a sweetener in carbonated beverages. In reviewing this petition, CFSAN evaluated potential harmful effects caused by the projected increase in aspartame's consumption and determined aspartame's stability in liquids. While CFSAN reviewers determined some breakdown of aspartame may occur in carbonated beverages, CFSAN concluded that aspartame and its breakdown products, at the increased consumption levels, posed no threat to safety.

CFSAN Raised Safe Consumption Level

With the use of aspartame in carbonated beverages, Searle estimated that the average daily consumption of products containing aspartame would significantly increase. For example, CFSAN projected that at the highest daily intake, 2- to 4-year- olds could potentially consume aspartame at almost 50 mg/kg of body weight.[1]

CFSAN reviewed five clinical studies submitted by Searle and five additional studies published in the literature to determine if this increased consumption was safe. Based on these clinical studies, CFSAN determined the regular consumption of aspartame at very high levels above 50 mg/kg/day did not result in any adverse effects. In addition, clinical studies conducted on adults, adolescents, children, diabetics, lactating mothers, infants, and obese and glutamate-sensitive individuals showed they suffered no adverse effects when consuming high doses of aspartame. Therefore, CFSAN concluded that the Acceptable Daily Intake could be raised from 20 to 50 mg/kg. At this higher level, a 132-pound person could drink about 15 cans of diet soda per day.

[1]50 mg/kg of body weight was 2.5 times the established Acceptable Daily Intake of 20 mg/kg.

Concern Over Aspartame's Breakdown Products

Searle's studies on aspartame's stability in carbonated beverages showed aspartame's effectiveness and safety during typical storage periods (up to 52 weeks), and over a range of temperatures—41 to 131 degrees Fahrenheit. CFSAN determined that under typical storage conditions (temperatures of 68 degrees Fahrenheit), aspartame remains relatively stable and maintains its taste acceptability. However, when exposed to more extreme storage conditions (high temperature and extended periods of time), aspartame's breakdown accelerates.

While CFSAN believed such storage conditions could be avoided by attention to handling and distribution, CFSAN acknowledged some aspartame breakdown in carbonated beverages was likely. In liquid form, aspartame decomposes into DKP, methanol, and its component amino acids (phenylalanine and aspartic acid). Therefore, CFSAN had to consider the safety of aspartame's breakdown products.

Under typical storage conditions, 3 to 4 percent of the aspartame added to carbonated beverages becomes DKP. Before the approval in 1974 of aspartame in dry foods, Searle completed a series of short-term DKP studies. After the 1974 approval, Searle submitted the Rat DKP Study and the Mouse DKP Study, considered crucial to the carbonated beverages' approval. Based on the results of these studies, CFSAN determined that even if all the aspartame in a carbonated beverage converted to DKP, the Acceptable Daily Intake of DKP would not be exceeded.

CFSAN also considered data on another of aspartame's breakdown products, methanol. Two scientists suggested methanol posed a significant threat to safety. CFSAN pointed out methanol is often formed during the consumption of many foods. For example, methanol is formed when one consumes fresh fruits and vegetables. CFSAN estimated that a breakdown of all the aspartame in a liter of aspartame-sweetened beverage would contain about one-third of the methanol level that might occur after consuming a similar quantity of fruit juice.

CFSAN also considered the potential toxic effects of phenylalanine and aspartic acid caused by increased consumption of aspartame. The PBOI had discussed similar issues with these products (see ch. 4). CFSAN concluded that even though consumption would increase with aspartame's use in carbonated beverages, these breakdown products would still not reach the levels identified as toxic.[2]

[2]Although the approval for use in carbonated beverages was not before the PBOI, estimates of aspartame's consumption used by the PBOI included carbonated beverages and other uses.

One issue receiving considerable CFSAN review concerned the potential for aspartame or its components to alter brain activity. A researcher contended that combined consumption of aspartame and certain carbohydrates could cause changes in brain function, thereby influencing human behavior, physical performance, or moods. After reviewing the researcher's data and data obtained from other related studies, CFSAN contended that this researcher's hypothesis was not supported.

After resolving the above issues to its satisfaction, FDA on July 8, 1983, approved aspartame's use in carbonated beverages.

Objections Raised

Shortly after the carbonated beverage approval, Mr. Turner and a scientist objected to the approval and requested a hearing to review their safety concerns. For example, the objectors speculated the amount of aspartame in carbonated beverages could increase the level of phenylalanine in the brain, resulting in behavioral changes. FDA denied the objectors' request, arguing that the PBOI had already addressed some of the objectors' issues and the information submitted by the objectors did not substantiate their safety concerns. The objectors filed suit against FDA for a hearing on carbonated beverages. However, the objectors lost their case in the federal district court and in the U.S. court of appeals, which affirmed the district court decision. The Supreme Court declined to hear the case. In 1986, FDA denied a petition from Mr. Turner to repeal its approval of aspartame for all uses. In January 1987, Mr. Turner petitioned the court of appeals to review FDA's denial of his petition.

Additional Uses of Aspartame Considered

FDA has received 16 petitions for aspartame's use in additional products. Six of them have been approved (see table 6.1). CFSAN did not require additional toxicological studies to determine the safety of these new uses. It determined that the consumption estimates and the stability tests for these new uses, together with the toxicological studies for the dry foods and beverage approvals, were sufficient for approval.

Table 6.1: Additional Petitions Approved for Aspartame's Use

Date filed	Petitioner	Use	Date approved
September 8, 1982	Rexall Corporation	Multivitamins	May 17, 1984
January 3, 1983	Coca-Cola Company[a]	As a sweetener in certain refrigerated noncarbonated single-strength and frozen concentrated beverages; and frozen stick-type confections and novelties	November 24, 1986
January 3, 1983	Tropicana Products, Incorporated[a]	Same uses as stated in the Coca-Cola Company's petition	November 24, 1986
December 8, 1983	Shaklee Corporation	As a sweetener in breath mints	November 24, 1986
January 20, 1984	Thomas J. Lipton, Incorporated	As a sweetener in tea beverages to include ready-to-serve, liquid concentrates and dry bases	November 24, 1986

[a]CFSAN reviewed these petitions simultaneously because they requested the same uses for aspartame.

For dry foods, beverages, and multivitamins, CFSAN calculated the Estimated Daily Intake at the 99th percentile.[3] However, if additional uses of aspartame were approved, CFSAN said it was unlikely a person would be a 99th percentile consumer for each aspartame use. In addition, for most food additives, FDA uses the 90th percentile for calculating consumption. Therefore, CFSAN concluded that the 90th percentile Estimated Daily Intake was more realistic. At the 90th percentile, these additional aspartame uses did not exceed the Acceptable Daily Intake level of 50 mg/kg.

In addition, in December 1983, in response to inquiries from drug manufacturers, the Center for Drugs and Biologics proposed a regulation to declare aspartame safe for use as an inactive ingredient in drug products provided certain labeling requirements were followed. FDA concluded that aspartame was safe for use in human drug products because the amount of aspartame used in these products would not contribute significantly to consumption of aspartame. On January 20, 1987, FDA published a final rule requiring drug products containing aspartame to be labeled to alert PKUs to the presence and amount of phenylalanine in the drugs. FDA included the amount of phenylalanine in the labeling because drugs, unlike food products, may not be optional for an individual.

CFSAN is currently considering proposals for aspartame's use in other products (see table 6.2). CFSAN officials told us they either have not completed their review of these petitions or have requested additional information from the petitioner.

[3]The 99th percentile refers to the level of consumption that would be exceeded on any given day by only 1 percent of those consuming aspartame.

Table 6.2: Petitions Filed for Additional Aspartame Uses

Date filed	Petitioner	Proposed use as a sweetener
July 27, 1983	G.D. Searle and Co.	Available to the consumer in bulk package form
January 20, 1984	Bernard Food Industries, Incorporated	In ready-to-serve gelatins, puddings, and fillings[a]
October 25, 1984	Squirt and Company	In ready-to-serve, nonrefrigerated, pasteurized, aseptically packaged dilute fruit juice beverages
May 13, 1985	Pfizer, Incorporated	In frozen desserts
June 28, 1985	Foodways National	In frozen cheesecake, fruit, and fruit toppings
June 18, 1986	Holland American Wafer Company	In wafer cookies
June 18, 1986	Canandaigua Wine Company	In wine coolers
June 18, 1986	Milk Industry Foundation, Beatrice Dairy Products, and The NutraSweet Company	Flavored milk beverages
August 29, 1986	The NutraSweet Company	In fruit spreads, toppings, and syrups
September 17, 1986	Milk Industry Foundation, Beatrice Dairy Products, and The NutraSweet Company	In yogurt products

[a]Originally this petition proposed the safe use of aspartame in ready-to-serve gelatin desserts. In December 1986, the petition was amended to provide for gelatins, puddings, and fillings.

FDA Monitors Aspartame's Safety

FDA's responsibility for aspartame's safety did not stop when it approved aspartame's use in dry foods, beverages, and other products. CFSAN monitors aspartame's safety through adverse reaction reports, consumption estimates, and research. To date, completed CFSAN evaluations of aspartame reports have not conclusively shown whether there is or is not a relationship between aspartame's use and the reported adverse reactions. Current surveys show aspartame consumption to be far below the Acceptable Daily Intake set by the beverage approval.

The majority of researchers responding to our questionnaire on aspartame were generally confident of aspartame's safety. Twelve of 69 respondents expressed major concerns over aspartame's safety; 10 believed aspartame should be removed from the market.

We identified 74 completed, ongoing, or planned studies on aspartame's safety. Ten respondents to our questionnaire believed additional research is needed on aspartame's neurological functions. In this regard, CFSAN recently funded a study on amino acids' and aspartame's neurological effects.

CFSAN Monitors Adverse Reactions to Aspartame

Following the approval of aspartame's use in carbonated beverages, FDA received an increasing number of reports concerning adverse reactions related to aspartame. The Centers for Disease Control reviewed these reports and, in November 1984, reported that it found no conclusive evidence that aspartame caused these adverse reactions.

FDA continues to receive adverse reaction reports on aspartame. In 1985, CFSAN established a centralized computer system to track and monitor adverse reactions to FDA-regulated foods and additives.

The Centers for Disease Control Reviews Adverse Reaction Reports

The number of adverse reaction reports on aspartame increased from 108 in the first 6 months of 1983 to 248 in the last 6 months of 1983. CFSAN suspected this increase might be related to widespread media attention on possible "side effects" of aspartame after the carbonated beverage approval. CFSAN concluded that the adverse reactions, such as headaches, dizziness, and mood changes, were generally not severe and showed no clear-cut association with aspartame consumption. However,

in February 1984, CFSAN asked the Centers for Disease Control to evaluate the adverse reaction reports because of the Centers' expertise in conducting epidemiological reviews.[1]

The Centers' preliminary review showed that many reports were missing key demographic characteristics of the complainants and essential information on symptoms. To obtain this missing information, FDA field staff used the Centers' developed questionnaire to interview individual complainants. The Centers' review had two primary purposes: (1) to provide a descriptive analysis of the reported symptoms and the characteristics of individuals reporting them; and (2) to determine the need for further clinical research.

The Centers performed reviews and data analyses on 231 cases. In its November 1984 report, the Centers concluded that

"... the majority of frequently reported symptoms were mild and are symptoms that are common in the general populace. While some reports are undoubtedly due to the coincidence of symptoms and aspartame consumption, and others may be due to the suggestibility of some persons, still others may be attributable to some as yet undefined sensitivity of some individuals to aspartame in commonly consumed amounts ... Although it may be that certain individuals have an unusual sensitivity to the product, these data do not provide evidence for the existence of serious, widespread, adverse health consequences attendant to the use of aspartame."

CFSAN Continues to Monitor Adverse Reaction Reports

In 1985, CFSAN implemented a computerized adverse reaction monitoring system to track adverse reaction reports from medical personnel, researchers, and consumers on aspartame and other food additives. This system gives CFSAN centralized information on potential problems caused by foods and food additives and a descriptive epidemiology of the reactions.

After CFSAN's initial review of adverse reaction reports, FDA district offices follow up on reactions determined to be severe and related to products containing aspartame. This follow-up includes developing a case report containing information from personal interviews with the individuals involved and related medical records, if available. FDA's Health Hazard Evaluation Board reviews the cases classified as severe and related to products containing aspartame. This board, which includes FDA epidemiologists, toxicologists, and physicians, routinely

[1]Reviews dealings with the incidence and distribution of disease in a population.

reviews adverse reactions to products and recommends regulatory action.

As of January 1987, CFSAN reported it received about 3,100 aspartame adverse reaction reports, not including the reports the Centers reviewed. Of these reports, CFSAN had completed its review of about 2,900. The district offices are following up on the remaining reports. Table 7.1 shows reported adverse reactions.

Table 7.1: Reported Adverse Reaction Reports

Symptom category	Number	Percentage
Neurological	1,045	23.6
Headache	983	22.2
Other	736	16.7
Gastrointestinal	668	15.1
Allergic	457	10.3
Behavioral problems	263	5.9
Seizures	175	4.0
No specified symptoms	96	2.2
Total	**4,423[a]**	**100.0**

[a]The total exceeds 3,100 because a complainant may have more than one reported symptom.

CFSAN reported about 9 percent of the reactions it had reviewed were severe. However, CFSAN concluded it cannot definitely state whether aspartame is or is not associated with the reported reactions. In most cases, the reactions are mild or moderate (e.g., headache and dizziness) with many confounding factors.[2] CFSAN officials cautioned that use of this type of information is limited when attempting to draw causal relationships between product consumption and reported reactions. Such relationships can only be clearly demonstrated through controlled clinical studies.

CFSAN Monitors Consumption of Aspartame

In response to the requirement in the 1981 aspartame approval (see ch. 5), Searle contracted with MRCA Information Services to provide CFSAN with data on actual aspartame consumption. MRCA began reporting to CFSAN in October 1982 and has provided quarterly updates and annual aspartame consumption reports.

MRCA's data are based on 2,000 households per year, reporting their actual food consumption for each member over 2-week periods. The

[2]Factors that contribute to a disease incidence.

periods are staggered throughout the year to account for seasonal variations. The data are reported for five different age brackets and are analyzed by percentile levels to allow monitoring of both average and heavy consumers of aspartame. Data are also provided for certain subpopulations, i.e., people on a diabetic diet, people on weight-reducing diets, and women of childbearing age.

In MRCA's most recent annual report (for the year ending June 1986), about 35 percent of the people were consuming aspartame products. The annual report showed the average daily consumption for all age groups was 5.6 mg/kg.[3] People on a reducing diet, women of childbearing age, and people on a diabetic diet did not exceed an average daily intake of 6 mg/kg. The 0- to 23-month-old group reported the highest average daily intake of aspartame at 20 mg/kg, or about 40 percent of FDA's Acceptable Daily Intake. In a 22-pound child, the amount of aspartame established as the Acceptable Daily Intake is equivalent in sweetness to 25 teaspoons of sugar daily. Therefore, the data show current aspartame consumption considerably below the Acceptable Daily Intake level established in the beverage approval (50 mg/kg).

Current Studies and Opinions on Aspartame

Although aspartame was approved for marketing over 6 years ago, some scientists believe additional research is needed. To obtain opinions on aspartame's safety and current research, we sent a questionnaire to 96 researchers. Sixty-nine responded. We categorized the responses by those researchers who said they have done or are doing aspartame research (43 respondents) and those that said they have not (26 respondents). Table 7.2 shows their overall responses.

[3]This consumption is calculated at the 99th percentile, which means that of those people consuming aspartame, 99 out of 100 consumed less than 5.6 mg/kg of aspartame daily. In this chapter, the consumption for all groups is calculated at the 99th percentile. We selected data from the 99th percentile because the Commissioner based his 1981 decision on consumption estimates for that percentile.

Table 7.2: Respondents' Opinions on Aspartame's Safety

Opinion on aspartame's safety	Aspartame researchers[a]	Others[b]	All respondents
Major concerns; little if any confidence in aspartame's safety	9	3	12
Somewhat concerned; generally confident of aspartame's safety	12	14	26
Few, if any, concerns; very confident of aspartame's safety	20	9	29
Did not respond to this question	2	0	2
Total	**43**	**26**	**69**

[a]Individuals who said they have conducted research on aspartame's safety.

[b]Individuals who said they have not conducted research on aspartame's safety.

Thirty-two respondents said their opinions were based, at least partially, on their research on aspartame. The basis for the remaining researchers' opinions included their review of others' research on aspartame, discussions with colleagues, and reviews of others' research on aspartame-related compounds.

Thirty-one respondents indicated that no additional actions should be taken on aspartame to protect the public. Six researchers did not respond to this question. Although 32 respondents indicated some type of action should be taken (see table 7.3), 22 did not indicate that aspartame should be banned, but rather suggested some other action to modify or inform the public on its use.

Table 7.3: Respondents' Opinions on Actions That Should Be Taken to Protect Consumers

Actions	Aspartame researchers[a]	Others[b]	All respondents
Require additional warning or quantity labels on products containing aspartame	15	7	22
Increase public awareness of the concerns about aspartame	13	7	20
Provide more information to medical personnel on suspected adverse reactions to aspartame	12	7	19
Limit the use of aspartame to certain populations	12	4	16
Limit the types of products containing aspartame	8	4	12
Withdraw the approval for use of aspartame in any food product	7	3	10
Other	6	3	9

[a]Individuals who said they have conducted research on aspartame's safety.

[b]Individuals who said they have not conducted research on aspartame's safety.

Note: The numbers will not add to 32 because respondents could indicate more than one action.

We also asked the respondents to indicate areas where research was needed on aspartame's safety. Eighteen of the researchers who had done or are doing aspartame research and 10 of the other researchers suggested areas needing further research. The areas mentioned most frequently were aspartame's effects on

- neurological functions (10 times),
- brain tumors (6 times),
- seizures (5 times),
- children (4 times),
- pregnant women (4 times), and
- headaches (3 times).

However, the respondents to our questionnaire indicated that 69 studies[4] on aspartame's safety are in progress or have been completed since 1981; 5 additional studies are planned. Table 7.4 indicates the types of studies and their status.

[4]This includes only research done in the United States (see ch. 1).

Table 7.4: Studies on Aspartame's Safety Identified by Respondents

Type of studies	Completed studies	Studies in progress	Planned studies	All studies
Animal	18	5	1	24
Clinical	22	14	2	38
Other	1	1	0	2
Unknown	2	6	2	10
Total	**43**	**26**	**5**	**74**

Nine of the 18 completed animal studies dealt with aspartame's effects on neurological functions. The others covered such topics as whether aspartame causes seizures, effects of chronic aspartame consumption, and effects of aspartame consumption on caloric intake. The 22 completed clinical studies included diabetics, infants, children, PKUs, and normal adults. The studies covered such topics as aspartame's effects on blood levels of amino acids, behavioral effects, aspartame and glutamate toxicity, and methanol levels caused by aspartame.

The five ongoing animal studies include research on aspartame's effects on blood pressure and the metabolism of aspartame's breakdown products. (See app. V for a list of the ongoing studies.) The 14 ongoing clinical studies address similar topics as the completed studies. The respondents indicated that 14 of all the ongoing studies should be completed by the end of 1987.

FDA has no requirement that it be notified of research on an approved food additive. However, The NutraSweet Company sends CFSAN the results of its aspartame studies, and CFSAN obtains results of other completed studies through literature searches or other researchers. The NutraSweet Company gave us the names of 16 completed studies and 4 ongoing studies performed in its laboratories, and CFSAN gave us information on one other study not identified through our questionnaire.

CFSAN is aware of studies in progress in each of the areas, except for brain tumors (see p. 71), mentioned by researchers as needing further aspartame research. Our questionnaire did not identify any research on whether aspartame causes brain tumors either. A CFSAN official said that CFSAN does not have sufficient evidence to require studies in any of the areas mentioned by the researchers. According to the official, the studies submitted by Searle for aspartame's approval supported its safety, and the information collected on adverse reactions and research performed since that time does not show the necessity for additional research. If CFSAN received sufficient evidence of a relationship between

an adverse reaction and aspartame, it could require The NutraSweet Company or other researchers to perform studies.

The director of CFSAN said information on the effects of amino acids and other dietary components as they relate to neurological functions would be useful. Therefore, CFSAN recently funded research to study neurochemical changes (including seizures) caused by amino acids. Aspartame will be included in this study. The objectives of this study are to

- develop an animal model that will enable the detection and interpretation of significant changes in brain function;
- determine the extent that consuming aspartame and other related compounds might result in changes of amino acid balance and brain function; and
- determine whether experimental conditions, such as routes of aspartame administration, affect neurochemical changes.

CFSAN indicated such a study is needed because "so little is known at this time about the inter-relationships between diet, neurochemistry and brain function." Although normal toxicological studies and the review process will detect some neurological changes, they may not detect more subtle changes in brain function and behavior. In addition, according to CFSAN, its "review of the literature on neurochemical and behavioral effects of aspartame indicates little consensus on the effects of this compound and the effects appear to depend to a large extent on the conditions used in the experiment." This study, CFSAN stated, will provide important baseline data, critical for determining the safety of related compounds. CFSAN hopes this study, which will take about 2 years to complete, will stimulate further research in the scientific community on the relationships between diet and brain function.

CFSAN is also planning a study, in conjunction with the National Institute of Environmental Health Sciences and the Air Force, to develop an approach for further neurobehavioral research. This approach would allow researchers to determine whether neurochemical changes in the brain caused by aspartame influence behavioral changes. No date has been set for its start.

Conclusions

To date, CFSAN has not determined whether there is a link between aspartame's use and reported adverse reactions, and market research

data for aspartame show actual consumption below the Acceptable Daily Intake.

We found through our questionnaire that researchers' opinions varied on aspartame's safety. However, most respondents who had major or some concerns on aspartame's safety did not propose that aspartame be taken off the market, but suggested other actions, such as labeling or increasing public awareness of their concerns.

The respondents indicated that research is needed on the effects of aspartame on neurological functions, seizures, brain tumors, headaches, children, and pregnant women. CFSAN officials are aware of ongoing aspartame studies in all these areas except brain tumors. They believe that aspartame's safety has been demonstrated but acknowledge that additional research would be useful.

Although over half of the researchers we surveyed expressed some concerns over aspartame's safety, we believe the research underway or planned by FDA and the scientists surveyed and FDA's monitoring of adverse reactions should help provide answers on aspartame's effects on certain subpopulations and neurological behavior. We believe such efforts should give FDA a basis for determining what future actions, if any, are needed on aspartame.

Agency and Other Comments

HHS commented that the report accurately and fairly represents FDA's actions regarding the approval of aspartame. The NutraSweet Company agreed with the report's findings, but did not believe our questionnaire results on aspartame's safety were representative of prevailing scientific community views.

We recognize that because we could not identify all researchers who have performed studies on aspartame, we could not project the results. However, we believe our questionnaire results provide useful information on the types of research needed, completed, and ongoing.

Mr. James Turner, a representative of the Community Nutrition Institute who has raised questions on aspartame's safety and objected to its approval since 1974, also commented on our report. Mr. Turner said our study was narrow and limited and left important questions about aspartame's safety unanswered. He commented that because we did not address scientific issues, our conclusions that FDA followed its process in approving aspartame are not creditable. He stated that previous GAO

reports on food additives dealt with scientific matters and the lack of FDA guidelines concerning food additive testing. He added that our current report's conclusions did not consider consumer reactions and scientific studies reporting adverse health effects associated with aspartame.

As indicated on page 16, we do not have the expertise to make scientific judgments on aspartame's safety or FDA's resolution of scientific issues. However, we do have the expertise to conclude that FDA followed its food additive approval process and to reach such conclusions without addressing scientific issues. In our two prior reports, we did not assess the validity of scientific issues but rather identified concerns raised by scientists both inside and outside of the government.

As noted in chapter 2, in the early 1970's FDA had no published guidelines outlining the types of food additive studies that needed to be conducted. Instead, FDA determined such requirements on a case-by-case basis. In 1982, FDA published guidelines for food additives which, according to FDA officials, formalized guidance that had been followed in the 1970's. Aspartame studies met the submission requirements of these guidelines.

In chapter 7 of our report, we discuss monitoring by FDA of reported adverse reactions, market research surveys showing aspartame consumption, and completed and ongoing aspartame research. We concluded that these actions should give FDA a basis for determining what future actions, if any, are needed on aspartame.

Since we do not have the expertise to make scientific judgments, we cannot comment on whether important issues surrounding aspartame's safety remain unresolved. However, we believe this report provides a comprehensive assessment of FDA's approval of aspartame and will give the scientific community an opportunity to independently judge whether FDA sufficiently addressed important scientific issues.

Questionnaire Results

This appendix shows how the 69 researchers who responded to our questionnaire answered each question. For each question in the general survey, the number next to each response is the number of researchers answering the question who chose that particular response. The letter "n" indicates the number of researchers who answered that question. For the questions on the study specific form, the number next to each response is the number of studies showing that particular response. The letter "n" indicates the number of studies for which the question was answered.

GENERAL SURVEY ON ASPARTAME STUDIES

NAME :_____

ADDRESS :_____

PHONE NO. :_____

SPECIALTY :_____

SAFETY. THIS SECTION ASKS YOUR OPINION ABOUT THE SAFETY OF ASPARTAME.

1. WHICH STATEMENT BELOW BEST DESCRIBES YOUR BELIEFS ABOUT THE SAFETY OF ASPARTAME? n=67

[12] 1. I HAVE MAJOR CONCERNS ABOUT THE SAFETY OF ASPARTAME; I HAVE LITTLE, IF ANY,CONFIDENCE IN THE SAFETY OF ASPARTAME.
[26] 2. I AM SOMEWHAT CONCERNED ABOUT THE SAFETY OF ASPARTAME; I AM GENERALLY CONFIDENT IN THE SAFETY OF ASPARTAME.
[29] 3. I HAVE FEW, IF ANY, CONCERNS ABOUT THE SAFETY OF ASPARTAME; I AM VERY CONFIDENT OF THE SAFETY OF ASPARTAME.

2. PLEASE DESCRIBE THE BASIS FOR YOUR CONCERNS ABOUT OR CONFIDENCE IN THE SAFETY OF ASPARTAME. n=62

_____

_____

_____

_____

_____

3. WHAT IS THE BASIS FOR YOUR CONCERN(S) ABOUT OR CONFIDENCE IN THE SAFETY OF ASPARTAME? **CHECK AS MANY AS APPLY.** n=64

[32] 1. YOUR RESEARCH ON ASPARTAME.
[49] 2. YOUR REVIEW OF OTHER RESEARCH ON ASPARTAME.
[25] 3. YOUR RESEARCH ON ASPARTAME RELATED COMPOUNDS.
[28] 4. YOUR REVIEW OF OTHER RESEARCH ON ASPARTAME RELATED COMPOUNDS.
[15] 5. LETTERS FROM CONSUMERS WHO USE ASPARTAME.
[32] 6. DISCUSSIONS WITH COLLEAGUES.
[8] 7. OTHER (PLEASE EXPLAIN)_____

_____

4. DO YOU BELIEVE ANY ACTIONS TO PROTECT CONSUMERS SHOULD BE TAKEN ON ASPARTAME? n=63

[32] 1. ACTION(S) SHOULD BE TAKEN.
[31] 2. NO ACTIONS SHOULD BE TAKEN.

IF YOU ANSWERED THAT NO ACTIONS SHOULD BE TAKEN ON ASPARTAME, PLEASE SKIP TO QUESTION #9 ON PAGE 3.

CASE #__ __ __

5. WHAT ACTION(S) TO PROTECT CONSUMERS, DO YOU BELIEVE SHOULD BE TAKEN ON ASPARTAME? **CHECK AS MANY AS APPLY.** n=32

[22] 1. REQUIRE ADDITIONAL WARNING OR QUANTITY LABELS ON PRODUCTS CONTAINING ASPARTAME.

PLEASE DESCRIBE_____

_____

[16] 2. LIMIT THE USE OF ASPARTAME TO CERTAIN POPULATIONS.

PLEASE DESCRIBE_____

_____

[12] 3. LIMIT THE TYPES OF PRODUCTS CONTAINING ASPARTAME. (CURRENTLY ASPARTAME IS APPROVED FOR DRY FOODS, CARBONATED BEVERAGES AND MULTIVITAMINS.)

PLEASE DESCRIBE_____

_____

[19] 4. PROVIDE MORE INFORMATION TO MEDICAL PERSONNEL ON SUSPECTED ADVERSE REACTIONS TO ASPARTAME.

PLEASE DESCRIBE_____

_____

[20] 5. INCREASE PUBLIC AWARENESS ON THE CONCERNS ABOUT ASPARTAME.

PLEASE DESCRIBE_____

_____

[10] 6. WITHDRAW THE APPROVAL FOR USE OF ASPARTAME IN ANY FOOD PRODUCT.

PLEASE DESCRIBE_____

_____

[9] 8. OTHER

PLEASE DESCRIBE More research is needed._____

_____

6. CAN ONE OR MORE OF THE ACTIONS YOU CHECKED ABOVE BE SUPPORTED BY YOUR RESEARCH? n=31

[19] 1. YES.
[12] 2. NO.

CASE #__ __ __

FOR THE FOLLOWING QUESTIONS, PLEASE CONSIDER ALL THE RESEARCH ON ASPARTAME OF WHICH YOU ARE AWARE.

7. WHAT CONCERNS, IF ANY, DO YOU HAVE ABOUT THE SAFETY OF ASPARTAME THAT YOU BELIEVE HAVE NOT BEEN OR ARE NOT BEING ADDRESSED BY CURRENT RESEARCH STUDIES? n=28

neurological functions(10) children(4)

brain tumors(6) pregnant women(4)

seizures(5) headaches(3)

8. WHAT CONCERNS, IF ANY, DO YOU HAVE ABOUT ASPARTAME THAT YOU FEEL CANNOT BE RESOLVED BY FURTHER SCIENTIFIC STUDIES? n=12

RESEARCH. THIS SECTION ASKS ABOUT ANY RESEARCH YOU HAVE PERFORMED ON THE SAFETY OF ASPARTAME.

9. PLEASE LIST YOUR RESEARCH PROJECTS ON ASPARTAME WHICH WERE COMPLETED AFTER 1/1/81, ARE IN PROGRESS, AND ARE PLANNED TO START IN THE NEXT YEAR. **IF YOU HAVE NOT DONE OR ARE NOT PLANNING ANY RESEARCH ON ASPARTAME, PLEASE CHECK HERE [27] AND SKIP TO QUESTION #10.** n=66

COMPLETED:

	TITLE:	DATE COMPLETED:
1.		
2.		
3.		

IN PROGRESS:

	TITLE:	ANTICIPATED COMPLETION DATE:
1.		
2.		
3.		

PLANNED:

	TITLE:	ANTICIPATED COMPLETION DATE:
1.		
2.		
3.		

PLEASE FILL OUT ONE STUDY-SPECIFIC FORM(SEE ATTACHMENTS PAGE 5) FOR EACH STUDY. IF YOU DO NOT HAVE ENOUGH FORMS, PLEASE MAKE COPIES OF THE BLANK FORM.

CASE #__ __ __

10. PLEASE LIST ANYONE ELSE YOU KNOW OF WHO IS PERFORMING OR HAS PERFORMED RESEARCH ON ASPARTAME THAT MIGHT NOT BE WIDELY KNOWN OR HAS UNPUBLISHED STUDIES ON ASPARTAME.

NAME	ADDRESS AND PHONE NUMBER
1.	
2.	
3.	

11. IF YOU HAVE ANY ADDITIONAL COMMENTS ABOUT THE SAFETY OF ASPARTAME OR RESEARCH ON ASPARTAME, PLEASE INCLUDE THEM IN THE SPACE BELOW.

Can the information provided by you be shared with the Food and Drug Administration? n=67

Yes__65__
No ___2__

CASE #__ __ __

STUDY SPECIFIC FORM

TITLE: COMPLETION(ANTICIPATED COMPLETION) DATE:

PLEASE ATTACH A COPY OF THE RESEARCH ABSTRACT/PROPOSAL FOR THIS STUDY. IN ADDITION, PLEASE DESCRIBE YOUR STUDY IN LAYMAN'S TERMS BELOW AND INCLUDE THE FOLLOWING:

1)HYPOTHESIS(PURPOSE)
2)NUMBER AND TYPE OF SUBJECTS
3)COMPOUND(S) TESTED
4)CURRENT STATUS
5)FINDINGS AND CONCLUSIONS

Total studies(74)

completed(43)

in progress(26)

planned(5)

1. IS FDA AWARE OF YOUR STUDY? n=58 1.YES 30 2.NO 5 3.CAN'T DETERMINE 23

2. HAS FDA COMMENTED ON YOUR STUDY? n=47 1.YES 3 2.NO 44

3. WHO IS FUNDING THIS STUDY? n=55 Searle=26 NIH=11

4. IF THE STUDY IS COMPLETED, IS IT PUBLISHED? n=52 1.YES 34 2.NO 18

5. IF THE STUDY WAS PUBLISHED, GIVE TITLE, DATE AND WHERE PUBLISHED.

Aspartame Studies Investigated

The 1975 task force, an FDA team, and UAREP investigated a total of 22 aspartame studies (see ch. 3). The FDA team and UAREP investigated five of the same studies as the task force. However, the FDA team and UAREP investigations were more detailed, identifying problems that had been previously noted by the 1975 task force as well as additional problems.

Table II.1 lists the studies and the group(s) that investigated each study.

Table II.1: Aspartame Studies Investigated

	Studies investigated by:		
Aspartame studies	**1975 task force**	**FDA team**	**UAREP**
Crucial studies:			
Two-Year Rat Study	X		X
Lifetime Rat Study			X
Two-Year Mouse Study			X
Long-Term Dog Study	X		X
Multigeneration Rat Study			X
Supplemental Dog Analysis			X
Supplemental Rat Analysis			X
Rat DKP Study	X	X	
Mouse DKP Study			X
Studies suggested by objectors:			
Newborn Rat Toxicity Study			X
Endocrine Studies			X
Pregnant Monkey Study			X
Other studies:			
Waisman Monkey Study	X		
Hamster Study	X		
Acute Rat, Mouse, and Rabbit Study	X		
Rat Teratology DKP Study Segment I	X		
Rat Teratology DKP Study Segment II	X		
Rabbit Teratology Aspartame Study Segment II	X		
Rabbit Teratology - Phenylalanine/Aspartic Acid Study Segment II	X		X
Mouse Teratology Aspartame Study Segment II	X	X	
Rat Teratology Aspartame Study		X	

Eleven Aspartame Studies Investigated by 1975 Task Force

The 1975 task force investigated 11 aspartame studies (see ch. 3) and uncovered "serious deficiencies in Searle's operations and practices which undermine the basis for reliance on Searle's integrity in conducting high quality animal research to accurately determine or characterize the toxic potential of its products." However, the task force said that unreliability in Searle's animal research did not imply its animal studies provided no useful information on the safety of the products, such as aspartame. They believed the FDA should conclude whether the results from a study could be used in evaluating a product's toxic potential. The remainder of this appendix consists of examples of the 1975 task force findings on the aspartame studies and CFSAN's comments.

Two-Year Rat Study

1975 Task Force Findings

Protocols did not specify the exact procedures for examining certain animals, and certain other experimental procedures were not followed.

The total number of tissues examined included autolyzed tissues, although these tissues should not have been used in calculating the percentage of incidence of certain types of lesions.

An observation from tissue slides was noted in a table of the final report for about 15 tissues. However, no tissue slides were noted as being prepared.

Animals were not tagged to prevent mix-ups.

The presence and the specific concentration of test compounds in the animal feed was not determined.

CFSAN Comments

Investigated by UAREP (see app. IV for comments).

Long-Term Dog Study

1975 Task Force Findings

Portions of Searle's submission to FDA were not supported by Searle's records. For example, the submission to FDA stated an evaluation of

	behavioral activity was routinely recorded, yet the task force could find no records for this. Feed containing the test compound was not assessed for homogeneity. Protocols were not always followed. The submission states that dogs ranged from 150 to 160 days of age, yet 3 dogs were 220 to 235 days of age. These three dogs were assigned to the treatment groups and none to the control group.
CFSAN Comments	Investigated by UAREP (see app. IV for comments).

Rat DKP Study

1975 Task Force Findings	Control and dosed animals were randomly distributed on the same rack and not tagged to prevent mix-ups. Feed containing the test compound was not checked for homogeneity, and food spillage by individual animals was not recorded. Some animals were not autopsied until 1 year after they died. Portions of Searle's submission to FDA did not include the animals' conditions during the study. For example, animals were infected with a disease during the study and medication was given, but this was not reported in Searle's submission to FDA. In some cases, protocols were not followed.
CFSAN Comments	Investigated by the FDA team (see app. IV for comments).

Waisman Monkey Study

1975 Task Force Findings

Protocols were written after the study was started and were not followed.

Portions of Searle's submission to FDA were not supported by Searle's records. For example, Searle's submission stated that animals were unavailable for autopsy at the study's termination. However, other documents indicated the animals were available, but Searle chose not to purchase them.

The exact intake of aspartame and DKP could not be calculated from the data submitted.

The Searle scientist listed as the primary author of the study's report was not employed at Searle until 3 months after the study was terminated.

CFSAN Comments

Two years before the task force report, CFSAN noted problems with this study because it was never completed, and the scientist in charge had died. CFSAN considered this study's findings to be of limited value, but indicated the study lent support to the need for labeling (see discussion on this study in ch. 2).

Hamster Study[1]

1975 Task Force Findings

Records of observations on animals were not accurate or consistent. For example, Searle was inconsistent in recording the dates showing when an animal died.

The primary author of the submission to FDA was not employed at Searle until 3 months after the study was terminated.

[1]This study includes three reports submitted to FDA. The 1975 task force investigated and counted the reports as one study.

CFSAN Comments	About 3 years before the 1975 task force report, CFSAN noted this study had been terminated before completion because of an infection in the animals. CFSAN found this study to be of limited value in evaluating the safety of aspartame before the 1975 task force review.

Acute Rat, Mouse, and Rabbit Studies

1975 Task Force Findings	Searle's submission to FDA could not be supported by Searle's records. For example, Searle reported the animals were observed over a 7-day period, which was not supported by data in Searle's records.
CFSAN Comments	CFSAN did not comment on the task force's findings. These studies were not considered to be "crucial studies" for the approval of aspartame.

Five Teratology/ Reproduction Studies

1975 Task Force Findings	The task force concluded that although transcription errors were found in all these studies, the errors would not significantly alter the reported conclusions.
CFSAN Comments	These studies were not considered to be "crucial studies" for the approval of aspartame.

Rat Teratology DKP Study (Segment I)

1975 Task Force Findings	The rats' dosage period was not accurately determined. The actual amount of DKP ingested by the rats could not be determined with certainty.

	On the basis of this study, it was not possible to set a "no adverse effect" level of DKP.
CFSAN Comments	CFSAN did not comment on the task force findings.

Rat Teratology DKP Study (Segment II)

1975 Task Force Findings	In spite of the poor reporting and minor inaccuracies, it was still possible to say DKP at levels as high as 2.4 percent was probably not toxic to the fetuses of the rats.
CFSAN Comments	CFSAN did not comment on the task force findings.

Rabbit Teratology Aspartame Study (Segment II)

1975 Task Force Findings	Conclusions on the effects of aspartame could not be properly assessed due to the poor design and the high animal death rate.
CFSAN Comments	About 3 years before the task force report, CFSAN noted this study precluded a meaningful evaluation of the high dose group for DKP because of the high death rate for animals in this group.

Rabbit Teratology Phenylalanine Aspartic Acid Study (Segment II)

1975 Task Force Findings	Animal groups received the incorrect test compounds throughout the study. However, this study was conceived and conducted at a satisfactory scientific level, and the problems found did not appear to be influential in interpreting the findings of the study.
CFSAN Comments	Reviewed by UAREP.

Mouse Teratology Aspartame Study (Segment II)

1975 Task Force Findings	The study used an inappropriate method of administering aspartame, limiting the conclusions that could be drawn. This study could only conclude daily doses of aspartame from greater than 0 to less than 2 grams would not have toxic effects on the fetus from the 6th to the 15th day of pregnancy.
CFSAN Comments	Reviewed by the FDA team.

Findings of the Reviews on Crucial Studies

In response to the 1975 task force findings, CFSAN selected 15 Searle aspartame studies for review (see ch. 3). UAREP reviewed 12 studies, 8 of which were crucial to aspartame's approval, and an FDA team reviewed 3 studies, 1 of which was crucial. The UAREP and FDA team reports contain many findings, some of which are discussed in this appendix.

UAREP's Comments on Searle's Studies

In carrying out its review of the aspartame studies, UAREP noted that when the Searle studies were performed (1970's), few standards for laboratory work were required. Therefore, UAREP stated it reviewed the studies using methods and interpretation common to research laboratories around 1970.

General Comments on All Studies

UAREP's general comments on issues addressed in the Searle studies follow.

- Animal Care Facilities: The American Association for Accreditation of Laboratory Animal Care had accredited the animal facilities at Searle since 1968 and at Hazleton Laboratories in 1971. UAREP said the fact both Searle and Hazleton had this accreditation while performing the aspartame studies "would indicate that their facilities were far above the average and would be considered quite adequate for that time."
- Personnel, Facilities, and Methods: UAREP stated "there have been many changes in personnel, facilities, and laboratory technology" since the aspartame studies were done. Although the great majority of the staff who carried out these studies were no longer employed by Searle or Hazleton, the scientific personnel with whom UAREP talked during visits to the laboratories exhibited good knowledge of their work and responsibilities.
- Protocols: UAREP found some of the studies' protocols appeared to be more a record of what had been done than a plan of what was to be done. However, UAREP concluded that the scientists knew what they were doing.
- Data Production, Handling, and Storage: UAREP agreed with Searle and Hazleton on more than 99 percent of the computations. They also found "a very small incidence of transcriptional discrepancies."

Although UAREP noted "a substantial number of minor and inconsequential discrepancies" during its review, it found "few, if any, discrepancies which would produce a change of greater than five percent in the final numerical data being compared." In addition, it did not find evidence

that, "given the experiment design, there was any indication that animals in any one group had been treated deliberately to produce biased results." The discrepancies it observed "appeared randomly distributed between treated and control groups."

CFSAN concluded that, although UAREP found some discrepancies in the aspartame studies reviewed, there were no discrepancies "that were of sufficient magnitude or of a nature that would compromise the data as originally submitted by Searle."

Four Long-Term Rodent Studies

In its report, UAREP grouped some of the eight crucial studies according to the studies' objectives and discussed its findings accordingly. For example, four long-term toxicity studies carried out by Hazleton tested the effects of aspartame or its breakdown product, DKP, in rodents. These studies were the Two-Year Rat Study, the Lifetime Rat Study, the Two-Year Mouse Study, and the Mouse DKP Study. UAREP's findings on these four studies follow.

- Clinical Observations: UAREP was "generally in close agreement" with Hazleton's clinical observations in these four studies.
- Body Weight, Food, and Compound Consumption: Based on the available data, UAREP "did not disagree" with Hazleton's handling of body weight and food consumption data. UAREP said its calculation of consumption at times differed from Hazleton's, but overall, both calculations were in "very close agreement."
- Survival Data: Although UAREP "generally agreed" with Hazleton's report that survival in dose groups was not statistically different, UAREP differed with Hazleton's values for percentage survival at the studies' ends. For example, in one study, this resulted because Hazleton killed animals in the high dose group 2 weeks earlier than animals in other groups and omitted 10 of these survivors in computing the average survival time.
- Clinical Laboratory Tests: These tests had "a scattering of statistically significant differences in various parameters and among various groups." However, UAREP agreed with Hazleton that "under the conditions of these experiments, these differences were neither dose nor compound related."
- Ophthalmoscopic Observations: UAREP noted some of the rats and mice had a clouding of the eye lenses, but found no dose relationship.
- Necropsy (Autopsy): UAREP found that on the basis of the information available, the autopsy records "were reasonably good," and it "generally agreed" with Hazleton's transcriptional and computational data.

UAREP pathologists evaluated the issue of autolysis noted by the 1975 task force. They found autolysis was randomly distributed among the studies' animals; therefore, they did not consider this to significantly affect the studies' results.

- Histopathology: UAREP pathologists examined 35,000 tissue sections without knowing the original diagnoses made by Hazleton's subcontractor. UAREP stated a "good correlation" existed between its diagnoses and those of the subcontractor. In addition, UAREP believed the differences noted and an occasional missing slide, "did not significantly affect" the results' interpretation. UAREP commented on the higher tumor incidence found in the controls and in the low dose groups, and said "there was no evidence that either aspartame or DKP enhanced the production of tumors in these studies."

Long-Term Dog Study

UAREP examined Searle's Long-Term Dog Study and commented on the following:

- Clinical Observations: UAREP was unable to evaluate the adequacy of clinical observation procedures in this study because it was not supplied with any records of clinical observation data.
- Body Weight, Food, and Compound Consumption: UAREP found the amount of aspartame consumed was "somewhat variable, but never was more than 6 percent from the desired dose." In addition, it said "the randomization of animals was done haphazardly" because two or three dogs from the same litter were in the same group, and the dogs with significantly higher body weights were in the high dose groups at the study's beginning.
- Clinical Laboratory Tests: UAREP noted "fewer significant differences" on blood tests between the dose and control groups than reported by Searle. However, Searle's data showed a significant number of red cells in the urine of some dogs. UAREP believed "these red cells would have produced bloody urine or resulted from urinary tract disease, but Searle's records did not report observing either bloody urine or urinary tract disease." Therefore, UAREP questioned the validity of these data.
- Ophthalmoscopic Observations: UAREP found two animals with cataracts, but determined these cataracts to be congenital.
- Necropsy (Autopsy): UAREP said the quality of tissue sections was generally good at the time of its review. In addition, UAREP found no discrepancies in Searle's transcription of organ weights from autopsy sheets to the report to CFSAN.

- Histopathology: UAREP's review of tissue slides showed "only two significant discrepancies" in the diagnoses when compared to Searle's diagnoses.

Supplemental Dog Analysis and Supplemental Rat Analysis

Because of a possible increased incidence of brain tumors in the Long-Term Dog Study, the Two-Year Rat Study, and the Lifetime Rat Study, Searle hired a pathologist to review additional brain tissue sections. The Supplemental Dog Analysis and the Supplemental Rat Analysis contained the results of the pathologist's review. UAREP convened a panel of experts to review the pathologist's findings on these studies. UAREP "agreed completely" with Searle's pathologist that there were no brain tumors in the dog brain tissue sections examined, nor other significant pathologic lesions relating to aspartame. In addition, they "generally agreed" with Searle's pathologist on the diagnoses of the rat brain slides and said "the 20 brain tumors diagnosed showed no statistically significant increase in any group when the tumors for the [Two-Year Rat Study and the Lifetime Rat Study] were combined."

Multigeneration Rat Study

Hazleton Laboratory performed the Multigeneration Rat Study reviewed by UAREP. UAREP noted "the consumption of aspartame was from 25 to 38 percent lower than planned at certain stages of the study." However, UAREP found "fewer discrepancies or problems in this study than in most of the other studies [it] reviewed."

FDA Team Comments on the Rat DKP Study

The FDA team examined one crucial study, the Rat DKP Study, and submitted its findings to CFSAN, which concluded that the concerns identified would not significantly alter the study's conclusions. This study was to determine DKP's safety and its potential to produce tumors. Some of the problems identified by the investigative team and CFSAN's comments are shown in table IV.1.

Table IV.1: FDA Investigative Team Concerns and CFSAN's Comments

Concerns identified by the FDA team	CFSAN comments
Eleven transcriptional errors were noted when comparing the organ weights from the original data with those weights submitted to FDA.	CFSAN used the corrected values in recalculating these data and found "the differences did not appear to significantly alter the submitted data."
The blood and urine data revealed 21 differences between Searle's submitted values and those in Searle's original data	CFSAN recalculated these data and found they "did not differ statistically" from the results Searle reported to FDA.
Searle did not report a third outbreak of an infectious disease to FDA.	CFSAN said this outbreak should have been reported. However, this disease only involved four animals, and records from the study showed no increase in the death rate of any group because of this infection. All surviving animals received treatment. These unreported facts "would not by themselves appear to affect the interpretation of this study."
The values to determine blood cholesterol were not reported for two days but appeared in Searle's records.	CFSAN calculated the unreported values and found they did not differ "significantly from the values reported for the other days."
Values to determine blood chemistries were not reported for two days, but appeared in Searle's records.	CFSAN said "although these values were not included in the submission to FDA, the omission would not appear to affect the results, since the findings are similar to those for the reported days."
In three instances, Searle's submission to FDA showed a pathology diagnosis for certain organs. However, Searle's records indicated these organs were missing.	CFSAN said the inclusion of any of the three diagnoses would not alter the conclusions.
Records of approximately 30 animals showed differences between the original pathology sheets and Searle's pathology summaries submitted to FDA. For example, several observations were omitted in the submitted data.	Although the omitted lesions should have been reported, CFSAN believed some of these lesions "could have been considered insignificant by some pathologists." CFSAN said the FDA investigative team pathologist's review of 20 percent of the tissue slides generally "showed agreement" between his findings and Searle's.
The protocol was not always followed. In many cases, the actual number of organs prepared was less than what was specified in the protocol.	CFSAN's review of Searle's data indicated many of the organs appeared to have been omitted due to autolysis. They said this loss was distributed among all groups and did not appear to be selective to particular organs or groups. CFSAN could not determine whether the results from this study "would have been altered" if these organs had been examined before autolysis.
Animals were not individually labeled; only the cages were labeled. In addition, the chances of administering the wrong diet to the animals was greatly increased by using unlabeled feeding jars.	CFSAN could find no evidence to suggest any feeding errors occurred. They could not determine whether any dietary mix-up occurred, because no feeding procedures existed for this study. However, they decided the increased incidence of uterine polyps and the decreased levels of blood cholesterol suggested mix-ups may not have occurred and the rats ate the DKP.

Concerns identified by the FDA team	CFSAN comments
A photograph was found in a Searle analyst's notebook which showed "discrete light-colored particles of varying sizes and shapes distributed nonuniformly throughout the feed." These particles were DKP. According to Searle's records, these samples were not homogeneous and had to be reground before sampling. The FDA team found no evidence these diets were reground before being fed to the rats.	CFSAN could not determine from the available information whether the diet was homogeneous and could not determine the actual amount of DKP consumed. Additionally, CFSAN stated the FDA investigative team could find no documentation on how the feed was prepared or whether these samples were representative of the rats' feed.
Differences in animal data were found between Searle's records and its submission to FDA.	CFSAN said these differences did "not appear to alter the interpretation of this study."
A tissue mass was removed from a high dose animal. In addition, incisions were made over tissue masses on two low dose animals, and the animals were continued in the study.	CFSAN said even though the removal of the mass from the high dose animal was reported to the FDA, "such an early excision can prevent the progression" to a malignant tumor. The masses on the two low dose animals appeared one week after the animal housing area was sprayed with a rodenticide, but these masses disappeared during the study.
At times, Searle changed the clinical laboratory procedures during the study.	CFSAN said Searle's submission should have reflected these changes in the procedures. Although it was "not unusual" to change a procedure during a study, CFSAN noted such a change could "conceivably result in differences" in the data. However, they concluded Searle's changes would "not appear to invalidate" this study.

Researchers Conducting Studies on Aspartame (as of the Fall of 1986)

Researcher	Location	Name of study
Bernard W. Agranoff, Ph.D.	University of Michigan	The Effect of Aspartame on Brain Amino Acid Uptake
Harold E. Carlson, M.D.	Northport Veterans Administration Hospital	Effect of Aspartame, if any, on Prolactin, Growth Hormone, Curisol, Insulin, and Glucose in Healthy Subjects
C. Keith Conners, Ph.D.	Children's Hospital of D.C.	Sucrose and Amphetamine in Children
Roger A. Coulombe, Jr., Ph.D.	Utah State University	Interaction of Aspartame and Antidepressant Therapy Possible Interactions of Aspartame in Hypertension
Susan Crane, Ph.D.	Rutgers University	Effects of Aspartame and Sucrose on Regional Brain Tyrosine, Norepinephrine, Dopamine in SHR and WKY Rats
David L. Horowitz, M.D., Ph.D.	University of Illinois	Ingestion of Aspartame without Food
Donald B. Hunninghake, M.D. Arthur S. Leon, M.D.	University of Minnesota University of Minnesota	Safety of Long-Term Aspartame Administration in Normal Subjects
Enid M. Knight, M.D.	Howard University	Effects of Aspartame on Rats Inoculated with Morris Hepatoma Cells
Anthony Kulczycki, Jr., M.D.	Washington University	Mechanism of Aspartame- Induced Allergic Reactions and the Natural History of Aspartame- Induced Hives
Timothy J. Maher, Ph.D. Richard J. Wurtman, M.D.	Massachusetts College of Pharmacy Massachusetts Institute of Technology	Aspartame and Seizures (many experimental models) Drug Interactions with Aspartame
Eugene H. Man, Ph.D.	University of Miami	Racemization of Amino Acids in Aspartame
Reuben Matalon, M.D., Ph.D.	University of Illinois	Aspartame's Effect on Carriers for PKU
William J. Pizzi, Ph.D.	Northeastern Illinois University	An Investigation of Induced Lowering of Convulsive Thresholds in Rodents Gabaergic Neural Function in Mice Treated with Excitotoxic Amino Acids
Robert H. Roth, Ph.D.	Yale University	Influence of Aspartame on Central Monoaminergic Systems
A. James Rowan, M.D.	Bronx Veterans Administration Medical Center	Clinical Study to Evaluate Seizures in Adults Allegedly Due to Aspartame Consumption
Susan S. Schiffman, Ph.D.	Duke University	Putative Headaches to NutraSweet
Donald L. Schomer, M.D. Richard J. Wurtman, M.D.	Beth Israel Hospital Massachusetts Institute of Technology	Epilepsy and Aspartame
Bennett A. Shaywitz, M.D.	Yale University	Effects of Aspartame on Children's Seizures Effects of Aspartame in Children Alleged to Have Seizures
Lewis D. Stegink, Ph.D. George L. Baker, M.D. Lloyd J. Filer, Jr., M.D., Ph.D.	University of Iowa Mead Johnson & Co. University of Iowa	Metabolism of Aspartame Degradation Products in Young Pigs Effect of Repeated Ingestion of Aspartame- Sweetened Soft Drinks Upon Plasma Amino Acid Concentrations in Individuals Heterozygous for Phenylketonuria Effect of Repeated Ingestion of Aspartame- Sweetened Soft Drinks by Normal Adult Subjects on Plasma Amino Acid Concentrations
Theodore B. Van Itallie, M.D.	St. Lukes Hospital, New York	Use of Aspartame Sweetened Foods to Study Further the Effect of Covert Calorie Dilution on Spontaneous Food Intake and Body Weight

Ongoing Studies Conducted Inhouse by The NutraSweet Company

26-week Rat Diet Mixture Study with Beta-aspartame

26-week Dog Diet Mixture Study with Beta-Aspartame

Metabolism/bioavailability of ^{14}C-beta-aspartame and ^{14}C-beta-aspartyl-phenylalanine in Rabbits

Metabolism/bioavailability of ^{14}C-beta-aspartame and ^{14}C-beta-aspartyl-phenylalanine in Dogs

Comments From the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

MAR 30 1987

Mr. Richard L. Fogel
Assistant Comptroller General
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Fogel:

The Secretary asked that I respond to your request for the Department's comments on your draft report, "Food and Drug Administration: Food Additive Approval Process Followed For Aspartame." The Department finds that the draft report accurately and fairly represented the Food and Drug Administration's actions regarding the approval of aspartame.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,

for Richard P. Kusserow
Inspector General

Comments From the Nutrasweet Company

The NutraSweet Company

Box 1111, 4711 Golf Road, Skokie, Illinois 60076
Telephone: 312/982-7000

March 27, 1987

Ms. Michelle Roman
U.S. General Accounting Office
Human Resources Division
Room 1-30, Park Building
12420 Parklawn Drive
Rockville, MD 20857

Dear Ms. Roman:

We have reviewed the draft of the forthcoming General Accounting Office report, provided to us for comment, that examined the process by which the U.S. Food and Drug Administration (FDA) approved the food additive aspartame.

In general, we are in agreement with the findings of the report as to the process by which aspartame was approved for use in the United States and the Company's participation in that process.

As we have stated previously, we do not feel that the results of the survey purporting to analyze scientific opinion on aspartame's safety are truly representative of the prevailing scientific opinions. Nevertheless, the majority of respondents felt that the safety of aspartame had adequately been addressed and that no further actions were required.

The criticisms and questions regarding aspartame have been reviewed and addressed on countless occasions not only by the FDA, but also other respected authorities such as The Scientific Committee for Food of the Commission of The European Communities, The Food Additives and Contaminants Committee of the United Kingdom, The Health Protection Branch of Canada and The Council on Scientific Affairs of the AMA. In each instance, these bodies have reaffirmed the safety of aspartame.

We thank you for this opportunity to express our views.

Sincerely,

L. Ivanauskas Mathews
Director
Regulatory Policy & Planning

LIM:da
1736f

Glossary

Amino Acids	Form the chief structure of proteins; several of them are essential in human nutrition.
Aspartic Acid	An amino acid that combines with phenylalanine to form aspartame.
Autolysis	A breakdown of all or part of a tissue, resulting in decay.
Confounding Factor	A factor that contributes to a disease incidence.
Control Animal	An animal subjected to the same conditions as the dosed animal except for the specific factor being tested.
Diketopiperazine (DKP)	A manufacturing by-product of aspartame and a breakdown product resulting from prolonged storage or increasing the temperature of products containing aspartame.
Epidemiological Reviews	Deal with the incidence and distribution of disease in a human population.
Experimental Design	The plan for conducting the experiment and is usually written in the protocol that is formulated before the experiment is begun.
Glutamate	An amino acid.
Histopathology	A branch of pathology concerned with tissue changes that accompany a disease. At the National Toxicology Program, this includes dissecting and examining test animals, preparing slides from animal tissues, and interpreting the slides.
Medulloblastoma	A brain tumor that usually occurs in embryonic tissue.

Mutagenicity Studies	Studies designed to determine if a substance causes genetic changes.
Neuroendocrine System	Relates to the nervous system and the endocrine (hormonal) system.
Neurotoxic	Poisonous or destructive to the nerve tissue.
Nitrosation	Occurs when certain chemicals combine to form nitrosamines, some of which are carcinogens.
Oncogenic	Giving rise to tumors or tumor formation.
Phenylalanine	A naturally occurring amino acid essential for optimal growth in infants and nitrogen equilibrium in adults; combined with aspartic acid forms aspartame.
Phenylketonuric (PKU)	An individual who has difficulty in metabolizing phenylalanine. This inherited disorder can cause mental retardation. Children born with this deficiency can develop into adults of normal intelligence, provided their condition is recognized soon after birth, and dietary treatment is started.
Protocols	Written plans for a scientific experiment.
Spontaneous Rate	The frequency of naturally occurring brain tumors found in rats not exposed to any test compound, such as aspartame. It is compared to frequency of brain tumors found in the dosed animals to determine whether the compound affects the frequency of brain tumors.
Teratology	Study of abnormal development and congenital malformations.
Uterine Polyp	A mass of tissue projecting from the normal surface level of the mucous membrane lining of the uterus.

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