REPORT OF THE COMPTROLLER GENERAL OF THE UNITED STATES

Regulation Of The Food Additive Aspartame

Food and Drug Administration AGC00148

Department of Health, Education, and Welfare

On July 26, 1974, the Food and Drug Administration published a regulation approving the use of aspartame, an artificial sweetener. Later, questions were raised regarding adverse effects of the additive on health.

Before these questions were answered, preliminary results of an agency investigation indicated discrepancies existed in the data submitted in support of aspartame's safety.

On December 5, 1975, the regulation approving the use of aspartame was suspended. Aspartame has not been, nor will it be, marketed until all questions about its safety have been answered.

MWD-76-111 APRIL 8, 1976

COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-164031(2)

The Honorable Gaylord Nelson
United States Senate RSN 00001

Dear Senator Nelson:

In your letter dated January 30, 1975, you requested that we review the Food and Drug Administration's (FDA's) methods for determining the safety of three additives--Food, Drug, and Cosmetic Red No. 2; saccharin; and aspartame--for use in food. You asked that we furnish separate reports on the three additives and that the reports focus on

--the history of FDA's regulation of the additives, including in-house and outside tests leading to a change in their regulated status;

--the current status of testing the additives and FDA activities affecting their status;

--the extent to which FDA has examined alternatives to the additives if their safety is questioned; and

--whether the regulatory action taken by FDA on these three additives, based on the scientific evidence available, complies with the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301).

We were also requested to determine FDA's legal authority for allowing a food additive regulation to remain in effect when scientific evidence has raised questions about the additive's safety.

This report on aspartame is the second of three reports to be issued. Our report entitled "Need To Establish The Safety of Color Additive FD&C Red No. 2" (MWD-76-40) was issued October 20, 1975.

In our review of aspartame, we concentrated on the period since February 1973, when a petition for its use was submitted to FDA for approval. We reviewed pertinent legislation, regulations, and practices relating to FDA's regulation

of food additives; examined FDA records relating to the regulatory status of aspartame; and reviewed documents submitted by its petitioner in support of the additive's safety. We interviewed officials of FDA; Canada's Food and Drug Directorate, Ottawa, Canada; and G. D. Searle and Company, Chicago, Illinois.

REGULATION OF FOOD ADDITIVES

Since enactment of the Food Additives Amendment of 1958 on September 6, 1958 (Public Law 85-929), the Federal Food, Drug, and Cosmetic Act has required FDA to establish regulations prescribing the conditions under which a food additive may be safely used.

The act (21 U.S.C. 348(b)(1)) provides that any person may file a petition with FDA proposing the issuance of a regulation prescribing the conditions under which an additive may be safely used. A 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 specimens of its proposed labeling.

--All relevant data on the physical or other technical effect the additive is intended to produce and the quantity of the additive required to produce such effect.

--A description of practicable methods for determining the quantity of the additive in or on food and any substance formed in or on food because of its use.

--Full reports of investigations made about the additive's safety, including full information on the methods and controls used in conducting the investigations.

In determining whether a proposed use of a food additive is safe, the act (21 U.S.C. 348(c)(5)) requires FDA to consider

--the probable consumption of the additive and of any substance formed in or on food through use of the additive;

--the cumulative effect of the additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in the diet; and

--safety factors generally recognized by qualified experts as appropriate for the use of animal experimentation data.

A food additive will be deemed unsafe and restricted from public use by FDA if available information fails to establish the safety of its proposed use or if it is found to induce cancer when ingested by man or animals (21 U.S.C. 348(c)(3)(A)).

WHAT IS ASPARTAME?

Aspartame--an artificial sweetener about 180 times as sweet as sugar--is a white, odorless, crystalline powder composed of 2 amino acids--L-aspartic acid and L-phenylalanine. Like sugar, aspartame produces about 4 calories per gram. However, because of its greater sweetness, when used in place of sugar, it provides only a fraction of the calories that would be provided by a quantity of sugar yielding equivalent sweetness.

G. D. Searle and Company developed aspartame in 1965 and arranged to market the sweetener jointly with the General Foods Corporation. However, as of February 1976, aspartame had not been marketed. Saccharin was the only approved artificial sweetener on the market.

PETITION TO MARKET ASPARTAME

Since June 1969 Searle representatives met several times with FDA officials to discuss requirements for a food additive petition proposing issuance of a regulation allowing the use of aspartame in food. FDA officials advised Searle of the requirements, including the need to submit the results of scientific studies supporting the safety of aspartame for its intended use.

On February 9, 1973, Searle submitted to FDA a petition proposing the issuance of a food additive regulation to provide for the use of aspartame in foods as a "* * * nutritive sweetener with flavor enhancing properties." The petition included general information on the characteristics and specifications of aspartame, its proposed uses, and summaries of scientific animal and human studies regarding its safety. The animal studies on aspartame included four long-term (46 weeks or more) toxicological feeding studies in four different animal species, one bladder implant toxicological study, several teratological and mutagenicity studies, and various pharmacological and metabolic studies. Also, animal studies on diketopiperazine (DKP) were submitted, including one bladder implant toxicological study and three short-term (up to 5 weeks) toxicological feeding studies. DKP is a manufacturing byproduct of aspartame and a breakdown product resulting from prolonged storage or cooking of products containing aspartame. The human research data included long- and short-term studies evaluating aspartame's effects when administered to healthy volunteers and persons with certain types of metabolic disorders and a study of the metabolism of DKP in human test subjects.

Aspartame's proposed uses included dry beverage mixes, gelatins, puddings, fillings, whipped toppings, presweetened breakfast cereals, carbonated beverages, and chewing gum.

On March 23, 1973, Searle amended its petition to request that the addition of the ingredient L-leucine (a water-soluble lubricant) be allowed in the tablet form of aspartame. This was to prevent the appearance of an unesthetic scum on the surface of liquids in which aspartame tablets would be used. L-leucine is listed in FDA regulations as a substance that is "generally recognized as safe" (21 C.F.R. 121.101 and 121.1002).

After reviewing the petition, FDA expressed concern about the following issues regarding animal studies, and on September 24, 1973, suggested to Searle that the petition be withdrawn unless the issues could be promptly resolved. No major issues were raised regarding the studies in humans.

--The potential of DKP or aspartame to combine with nitrites in the stomach to form nitrosamines, some of which are known carcinogens. (This combination is known as nitrosation.)

--The adequacy of data to determine the significance of certain pathological findings, such as brain tumors and liver and kidney changes noted in some test animals used in a lifetime study and a neonate (newly born) rat study.

--The significance of the increased incidence of hyperplasia (the abnormal increase in the number of cells in the normal arrangement in a tissue) in mice exposed to aspartame and tumors observed in the urinary bladders of mice exposed to DKP in separate 26-week urinary bladder implant studies.

--The adequacy of data to determine the long-term effect of DKP. FDA considered the three short-term toxicological DKP feeding studies submitted by Searle to be of limited value in assessing DKP's long-term safety.

In response to FDA's letter, Searle provided the following data.

--On January 14, 1974, Searle submitted data on the nitrosation potential of aspartame and DKP based on a study of compounds that were structurally similar but not identical to aspartame or DKP using simulated physiological conditions. According to FDA's Division of Toxicology, the study showed that the compounds were extremely unstable in water which "would preclude the nitrosation of APM [aspartame] or DKP under physiological or aqueous conditions." Thus, FDA did not consider nitrosation of aspartame or DKP to be a problem.

--Also on January 14, 1974, Searle submitted the results of a second lifetime aspartame study involving rats. Based on this study, FDA concluded that the brain tumors and kidney changes observed in some of the test animals in the first lifetime and neonate rat studies did not appear to be dose related. The results of the new study indicated the presence of liver nodules (small knots or swellings) in some test animals. FDA concluded that the nodules' presence were not statistically significant and attributed them to a "fortuitous occurrence in this experiment" rather than to the feeding of aspartame.

--On January 31, 1974, Searle submitted final reports on two 56-week urinary bladder implant toxicological studies using mice. The studies' results indicated no significant difference in the incidence of tumors in the urinary bladders of mice treated with aspartame or DKP as compared to the incidence of such tumors in untreated control mice. FDA concluded that "Neither APM [aspartame] nor DKP are tumorigenic by this test system."

As of January 1974 Searle was conducting long-term DKP feeding studies. (See p. 11.)

RESTRICTED USE OF ASPARTAME APPROVED

On July 26, 1974, FDA published a regulation approving the use of aspartame in certain foods. Because prolonged exposure to cooking temperatures can cause significant breakdown of aspartame to DKP, the regulation did not approve any use of aspartame which could result in any appreciable breakdown to DKP. FDA approved aspartame's use 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 2 teaspoonfuls of sugar.

--Sugar substitute tablets for sweetening hot beverages, including coffee and tea. (L-leucine was approved for use in the tablets at a level not to exceed 3.5 percent of the tablet's weight.)

--Cold breakfast cereals.

--Chewing gum.

--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.

Because L-phenylalanine, contained in aspartame, can be harmful to individuals having phenylketonuria (a genetic defect in metabolism), the statement "PHENYLKETONURICS: CONTAINS PHENYLALANINE" was required on all food products' labels containing aspartame. Also, the regulation provided that when aspartame was used in a sugar substitute for table use, its label must instruct against use in cooking or baking.

The Federal Register notice concerning the regulation, stated that of principal importance to the Commissioner's judgment of aspartame's safety, as regulated, were two long-term feeding studies using rats and dogs. It noted that these two studies revealed a "no-effect" level (the maximum level of exposure without a statistically significant adverse effect) for aspartame at least as high as 2 grams per kilogram of body weight. The notice pointed out that by using a 100-fold safety factor and applying the no-effect level to the average 60-kilogram (about 132 pounds) man, an acceptable intake level would be at least 1.2 grams of aspartame a day. FDA's general regulation (21 C.F.R. 121.5) provides that a safety factor of 100 to 1 should be used when applying animal experimentation data to man.

Based on the restrictions imposed by its regulation on aspartame's use, FDA calculated that an individual's daily consumption level would not likely exceed 1.3 to 1.7 grams a day. FDA's calculations were based on the intake of the following foods sweetened with aspartame as shown in the table on the following page.

According to the Federal Register notice, because of the conservativeness of the no-effect level derived from the animal tests and the 100-fold safety factor employed in relating the tests to man, FDA believes that the uses approved by its regulation constitute an acceptable daily intake of aspartame with an ample margin of safety.

OBJECTIONS FILED AGAINST ASPARTAME

The act provides individuals adversely affected by a food additive regulation the opportunity to file objections and request a formal public hearing (21 U.S.C. 348(f)(1)). These objections must be filed with FDA within 30 days after the regulation's publication specifying the

provisions of the regulation which are objectionable and the reasons for the objections. If FDA determines that there are reasonable grounds for the objections, it is required to convene a public hearing promptly and consider all evidence and relevant material supporting the objection. FDA may stay the regulation if it determines the objections warrant it.

Aspartame approved use	FDA's estimate of daily intake (grams)	
	Low	High
As a table top sweetener in coffee or tea with an estimated .083 grams of aspartame per 8-ounce cup--drink 3 cups a day	.250	.250
In a dry beverage mix with .725 grams of aspartame per quart--drink 1 quart	a/.650	.725
In a gelatin dessert mix with 1.04 grams of aspartame per 2 cups dessert or .26 grams of aspartame per 1/2 cup serving--eat 1 to 2 servings	.260	.520
In a whipped topping with .15 grams of aspartame per 2 cups topping or .038 grams of aspartame per 1/2 cup serving--eat 1 to 2 servings	.038	.075
In a presweetened breakfast cereal with .083 grams of aspartame per 1-ounce cereal--eat 1 to 1-1/2 ounces cereal	.083	.125
Total	1.281	1.695

a/To arrive at the low estimate, FDA assumed there would be 1.3 grams of aspartame in 2 quarts of dry beverage mix or .650 grams per quart.

Within 30 days of FDA's July 26, 1974, regulation approving the restricted use of aspartame, three statements of objection 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 another jointly by James S. Turner, Washington, D.C., and Legal Action for Buyers' Education and Labeling, Inc. (LABEL, Inc.), Washington, D.C.

The Quaker Oats Company did not request a hearing but objected to the requirement that cold breakfast cereals containing aspartame bear on their product labels the statement PHENYLKETONURICS: CONTAINS PHENYLALANINE. The company stated that the amount of phenylalanine contributed by common protein-containing ingredients in cold breakfast cereal is about three times that contributed by aspartame if added as a sweetener. The company contended that such a statement would be "unnecessary and redundant" and requested that the regulation be changed to allow the omission of the statement on cold breakfast cereals containing aspartame.

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

The other objectors' concerns focused primarily on the possible adverse effect of aspartame on infants and young children who, the objectors' believed, would be the major consumers of foods containing the sweetener. Dr. Olney said that large doses of aspartame or combined doses of aspartame and monosodium glutamate, another food additive, could cause brain damage in infants and young children. He claimed that, based on research done by himself and others, L-aspartic acid (a component of aspartame) exhibited the same toxic response in the brain as exhibited by monosodium glutamate in earlier studies. He stated that the neurotoxicity (poisonous to the nervous system) of the substances is augmented when they are combined. Dr. Olney requested a public hearing to examine aspartame's toxicity.

Regarding Dr. Olney's objections, the Bureau of Foods believed that large doses of aspartame would not be consumed by infants and young children if the FDA aspartame regulation restricting its use was followed. The Bureau noted that L-aspartic acid and monosodium glutamate can

act similarly and are of about equal potency but did not agree that their effect would be augmented when combined.

Mr. Turner and LABEL, Inc., also expressed concern about the potential harmful effects of aspartame to infants and young children. They cited findings of a primate study which showed that at high feeding levels (3 and 4 grams of aspartame per kilogram of body weight), infant monkeys experienced grand mal-type seizures (a form of epileptic attack). They claimed that the monkeys ate aspartame-sweetened formula only to the level of sweetness they enjoyed, refusing food at higher levels; nevertheless, the highest level of sweetness accepted caused grand mal-type seizures.

Mr. Turner and LABEL, Inc., expressed concern that consumption of aspartame by pregnant women could cause mental retardation in their offspring. They cited a study with monkeys which showed that amino acids crossing the placenta tended to be concentrated in the blood of the fetus at higher levels than in the blood of the mother. They noted the researcher's speculation that, in some cases, this phenomenon might be responsible for mental retardation in the offspring. Mr. Turner and LABEL, Inc., requested that the regulation approving aspartame be stayed pending a public hearing or withdrawn completely.

Responding to the objections from Mr. Turner and LABEL, Inc., a Bureau of Foods' Division of Toxicology official stated that contrary to the objectors' comments, infants do not discriminate by taste but consume food until satisfied as long as it is pleasing. He stated that, by using a safety factor to convert the no-effect level of aspartame found in animal studies to humans, it was estimated that a 20-pound child could safely consume up to 475 packets of aspartame daily (each equivalent to 1 teaspoon of sugar). The Bureau noted that human infants are incapable of helping themselves to aspartame or aspartame-sweetened food and that they were unaware of any reliable evidence that children above the age of 1 year would be adversely affected by aspartame.

The Bureau said that there was no evidence of actual harm resulting from differing levels of amino acid concentrations in the blood of the fetus and of the mother.

After reviewing all the objections, the Bureau concluded that the uses of aspartame authorized by the regulation were safe, considering a reasonably exaggerated intake by children and adults. The Bureau recognized, however, that there were differences of opinion between FDA and the objectors which justified a hearing.

All parties to the proposed hearing agreed that the following questions should be addressed.

--Does aspartame pose a risk of contibuting to mental retardation or other brain damage and, if so, should approval of aspartame be withdrawn since available data fails to establish that the use of aspartame specified in the regulation would be safe?

--Do aspartame and monosodium glutamate have a combined toxicity and, if so, should approval of aspartame for use in children's foods be withdrawn since available data fails to establish that such use as specified in the regulation would be safe?

--Do aspartame and monosodium glutamate have a combined toxicity and, if so, what label warning statements, if any, would be appropriate if the approval of aspartame is not withdrawn?

SUBSEQUENT STUDIES BY SEARLE DELAY HEARING

On October 22, 1974, about 3 months after the aspartame regulation was issued, Searle submitted to FDA the results of three long-term toxicity feeding studies involving DKP and aspartame. These studies included a 104-week toxicity feeding study of aspartame in mice, a 110-week toxicity feeding study of DKP in mice, and a 115-week oral tumorigenicity study of DKP in rats. The Bureau of Foods' Division of Toxicology evaluated these studies and, in an April 16, 1975, memorandum, concluded that the two mice studies generally did not produce compound-related toxic or tumorigenic effects.

In the 115-week DKP study, six groups of rats--three groups of male and three groups of female--were fed DKP at levels of .75, 1.5, and 3.0 grams per kilogram of body weight per day. Two groups of rats--one male and one female--were not fed DKP. This 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 DKP at the two highest levels as compared to rats not fed DKP. According to a division of pathology memorandum dated July 28, 1975, the carcinogenic potential of these polyps required evaluation.

FDA suspended further consideration of holding a hearing, and Searle and General Foods voluntarily agreed to withhold marketing aspartame until the carcinogenic potential of the polyps could be resolved. Independent pathological evaluations of the uterine polyp tissues were made by teams of (1) FDA pathologists, (2) Armed Forces Institute of Pathology pathologists at the request of FDA, and (3) consultants selected by Searle. Each review team concluded that the polyps were not "cancerous, percancerous or potentially cancerous." However, Dr. Olney, Mr. Turner, and LABEL, Inc., expressed concern about the carcinogenic potential of the polyps and requested that this issue be added as a fourth question to be considered when the hearing was convened. FDA agreed with the request.

FDA QUESTIONS DATA SUBMITTED BY SEARLE

Besides manufacturing aspartame, Searle also manufactures a number of drugs which FDA has approved for marketing. In July 1975 FDA raised questions about Searle's performance of animal experiments and its reporting of safety data to FDA concerning two drugs--flagyl, used to treat infections and aldactone, an antihypertension drug. Because of the importance and sensitivity of these questions, the FDA Commissioner, on July 23, 1975, established a Searle Investigation Task Force to

--review the practices followed by Searle in conducting animal experiments, analyzing the experiments' data, and submitting the data to FDA;

--determine if there is evidence that any practices of Searle in carrying out the above functions violated the Federal Food, Drug, and Cosmetic Act or any other laws of the United States; and

--recommend an appropriate course of action based on the investigation's findings.

FDA officials said that the investigation was directed primarily toward evaluating drug data submitted to FDA since 1968. They stated that the review of aspartame data was included as part of the investigation, however, because (1) of the additive's recent approval, (2) of its potential for wide use in foods, and (3) its inclusion would provide a broader product base to evaluate Searle's practices.

ASPARTAME REGULATION STAYED

Preliminary results of the task force investigations indicated possible discrepancies in the data and the research summaries submitted to FDA supporting aspartame's safety. On December 5, 1975, FDA stayed the regulation approving the use of aspartame pursuant to authority contained in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348(e)) which states:

> "Any order, including any regulation established by such order, * * * shall be published and shall be effective upon publication, but the Secretary may stay such effectiveness if, after issuance of such order, a hearing is sought * * *."

On January 20, 1976, the FDA Commissioner disclosed the preliminary task force findings at joint hearings before the Senate Subcommittees on Health and on Administrative Practice and Procedure, Committees on Labor and Public Welfare, and the Judiciary, respectively. The Commissioner stated that 11 studies submitted supporting the food additive petition for aspartame had been reviewed and numerous problems had been noted. For example, he stated that in a 115-week rat study FDA investigators found

> "* * * poor methods of distribution and identification of control and treated animals, * * * poor records of weighings, * * *. Approximately 90 of the 196 animals that died during the study were fixed in toto [preserving animal organs without separation from the body] and necropsied [examined post mortem] at some later date; in some cases more than one year later.
>
> "Searle's practice of fixing animals in toto and not necropsying them for several months is not established as an accepted procedure."

Also, the Commissioner stated that data submitted to FDA on the results of this study was not consistent with the data in Searle's records for the study. He said that Searle's records on test animals used in the study

> "* * * indicated that a high dose female found dead during the experiment contained a tissue mass. The submission to the FDA reported no such tissue mass and the animal was excluded from the study * * *."

The Commissioner further stated that a review of the records for a number of animals disclosed significant discrepancies between Searle's pathology sheets and pathology summaries submitted to FDA.

The Commissioner testified that in reviewing five reproduction and teratology studies for aspartame, FDA investigators found "* * * poor animal husbandry practices and problems in the design of some of the studies." He stated regarding another study reviewed by the investigators--a 104-week rat study--that in at least four instances lesions were noted in gross necropsy but no slides were made of these lesions for histopathological (study of tissue changes caused by disease) examination. He stated that the investigators also found that a pathologist's summary was "* * * edited in such a manner as to alter, generally in a favorable direction, some of the pathologist's summarized findings."

The FDA Commissioner said that a final decision on whether to revoke the regulation approving the use of aspartame would be made after the task force has officially completed its investigation. The Commissioner added, "In no event will the additive [aspartame] be permitted to be remarketed until all questions that have been raised about its safety have been aired and resolved."

A Bureau of Foods official told us that if the regulation is not revoked, the hearing would be scheduled. He stated that the staying order would most likely not be lifted by FDA until the hearing is held and the safety questions raised regarding the original regulation are resolved. Should the regulation be revoked, the hearing on the scientific issues would be unnecessary; however, the petitioner would then have the right to request a hearing to review the basis for the petition's revocation.

As requested by your office, we have not obtained the Department of Health, Education, and Welfare's written comments on the matters in this report. However, we have discussed these matters with FDA officials and have considered their comments.

Sincerely yours,

R. F. Keller

ACTING Comptroller General
of the United States

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