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ARTIFICIAL SWEETENERS

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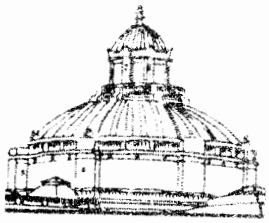

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ISSUE DEFINITION

Artificial sweeteners have been a source of controversy in the U.S. for over 70 years. The safety of three low calorie sweeteners -- cyclamate, saccharin, and aspartame -- continues to be debated. Driving these issues has been an interplay of a large consumer demand for low calorie sweeteners and controversy concerning certain safety standards set forth in the Food, Drug and Cosmetic Act (FDCA).

Current artificial sweetener issues include the following: 1) Cyclamate -- dispute concerning the validity of studies that led to the 1970 ban of cyclamate has prompted some groups to seek reapproval of the additive; 2) Saccharin -- because saccharin has been determined to be an animal carcinogen and therefore its use as a food additive is contrary to the "Delaney clause" of the FDCA, and because aspartame is an approved alternative, the prudence of continuing to permit marketing of saccharin via extensions of the Saccharin Study and Labeling Act has been questioned; 3) Aspartame -- the quality of the research and FDA approval process which brought aspartame to the market in 1981 has been questioned and is currently under investigation by the General Accounting Office (GAO). Finally, underlying some of the safety issues specific to artificial sweeteners is a debate concerning the appropriateness of the food additive safety standard embodied in the controversial "anti-cancer," or Delaney, clause of the FDCA.

As the artificial sweetener debate continues, policymakers may wish to consider the appropriateness of the food additive safety standards of the FDCA, including the Delaney clause, and the impact of these standards on the nature of substances that are approved and denied approval under the FDCA; the appropriateness of continued extensions of the Saccharin Study and Labeling Act in light of the approval of aspartame; and the appropriateness of the evaluations made by FDA which eventually led to the ban of cyclamate and the approval of aspartame. This issue brief provides background information on the FDCA provisions most pertinent to artificial sweeteners, highlighting the Delaney clause controversy; and, analyzes scientific and policy issues concerning cyclamate, saccharin, and aspartame.

BACKGROUND AND POLICY ANALYSIS

Regulation of food additives, including artificial sweeteners, is carried out by the Food and Drug Administration (FDA) according to the authority conferred by the FDCA. Food regulation originated with the Pure Food and Drug Act of 1906 which deemed food to be adulterated if it contained "any poisonous or deleterious ingredients which may render such article injurious to health." Later, the Federal Food, Drug and Cosmetic Act of 1938 (FDCA) expanded the definition of adulterated food to include foods containing

> any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance, such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health. [FDCA section 402 (a)(1)].

In 1958, the FDCA was amended to address specifically the safety of food additives through the Food Additives Amendment. Many different substances are considered food additives in a colloquial sense, but a substantial number of these are excluded from the strict definition of "food additive" provided in the FDCA as a result of this amendment. According to the legal definition, "food additive" refers to "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food...."

The law not only defines "food additive," but describes specific exceptions to the definition of food additive. The exceptions according to the FDCA are: 1) pesticide chemicals used in the production, storage, or transport of raw agricultural commodities; 2) substances that accidentally or unavoidably get into food; 3) color additives; 4) new animal drugs; 5) prior sanctioned substances, i.e., added substances with approval prior to enactment of the 1958 Food Additives Amendment; and (6) "GRAS" substances, i.e., added substances generally recognized as safe [FDCA section 201]. Substances that belong to one of the above listed categories are not subject to the FDCA provisions specific to "food additives." The artificial sweeteners saccharin and aspartame are considered food additives. However, cyclamate was a GRAS substance in 1969 when FDA initiated regulatory action restricting its use.

The Food Additives Amendment set up a premarket approval system for food additives [FDCA section 409 (b)(1)]. The system placed the burden of proof concerning additive safety on the industry or petitioner seeking additive approval. The petitioner must establish food additive safety under the proposed conditions of use by submitting appropriate studies to FDA. The FDCA does not specifically define the term "safe," but does limit application of the term to refer solely to the "health of man or animals" [FDCA section 201 (u)]. Before the amendment, FDA held the burden for proving an already used additive unsafe.

Another important provision of the Food Additives Amendment is the controversial "anti-cancer," or "Delaney" clause. This clause applies only to carcinogenic food additives, but similar anti-cancer clauses appear in the FDCA sections that pertain to color additives and animal drugs [sections 706 (b)(5)(B) and 512 (d)(1)(H), respectively]. FDA is prohibited from approving the use of carcinogenic food additives [FDCA section 409(C)(3)(A)]. The following anti-cancer language pertains to food additives.

> Provided, that no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evalution of the safety of food additives, to induce cancer in man or animal, [FDCA section 409 (c)(3)(A)].

THE DELANEY CONTROVERSY

Several different views exist concerning the value and appropriateness of the Delaney clause. Historically, this controversy has been an undercurrent in many food safety issues, including the artificial sweetener issues. In 1977, FDA proposed the ban of saccharin under the Delaney clause. Cyclamate was banned in 1970 under the general food safety provisions of the FDCA, but the existence of the Delaney clause played a key role in the cyclamate decision. In addition, the Delaney clause could apply to other artificial

sweeteners in the future if evidence demonstrates them to be carcinogens. Therefore, a brief analysis of the Delaney debate is in order.

Positions concerning the Delaney clause can be broadly grouped into three categories: opposition to the clause, support for the clause, and the belief the clause is of little consequence. In general, Delaney critics believe the clause has become antiquated as modern technical capability has made detection of increasingly small amounts of food carcinogens possible. Critics object to the fact that the Delaney clause is an absolute prohibition of carcinogenic food additives and does not take into account the potency or dose of the carcinogen, or distinguish between animal and human carcinogens. The Delaney clause is said to be a "zero risk" standard. Because many Delaney critics believe that not all carcinogens pose equal risks to humans, they advocate the use of "quantitative risk assessment" instead of the Delaney clause to regulate carcinogenic food additives.

Risk assessment is a method of analyzing scientific data using the potency and dose of a substance to estimate mathematically the risk posed to public health. The risk estimate can then be used by regulators to decide whether or not the substance should be approved. The regulatory decisionmaking process is referred to as risk management. Risk assessment and management is already used to regulate many food safety and other public health hazards.

In general, advocates of the Delaney clause believe the clause offers better protection to public health than risk assessment would. The clause is said to encourage caution in food additive regulation. While only two food additives have been banned under the clause, (Flectol H and 2-choroanaline), advocates argue the clause has been important in preventing approval of potentially hazardous food additives. Many Delaney advocates also distrust risk assessment for evaluation of carcinogenic food additives because different mathematical models can produce different risk estimates for the same substance. In addition, many are concerned that too little is known about cancer, and possible cumulative or synergistic effects of carcinogens to be accounted for in a risk assessment.

Another perspective concerning the appropriateness of the Delaney clause is that the clause is redundant with the general safety provisions of the FDCA. The Senate report that accompanied the 1958 Food Additives bill stated that the intent of the legislation was to prevent the addition to food of any substance causing, not only cancer, but any disease or disability. The report further stated that the Food Additives bill read and meant the same with or without the Delaney clause (S. Report no. 2422, 85th Congress, 2d session, 1958). More recently, this perspective has been reiterated by some food law experts. The fact that only two food additives have been banned under the Delaney clause since 1958 is sometimes cited as evidence that the Delaney clause is less consequential than the public debate might suggest.

CYCLAMATE

The term "cyclamate" refers to several chemical derivatives of cyclohexylsufamic acid which are approximately 30 times sweeter than table sugar. Unlike table sugar, cyclamate is considered a "non-nutritive" sweetener because the body cannot extract energy from it. Cyclamate was introduced in 1937 and was approved as an over-the-counter drug for the dietary management of obesity and diabetes in 1951. Cyclamate was subsequently produced by Abbott Laboratories and marketed as a table-top sweetener under the trade-name "Sucaryl."

The more potent artificial sweetener, saccharin, had already been on the market for many years but consumption was limited because it had an unpleasant aftertaste. Following the approval of cyclamate, it was learned that a 10 to 1 mixture of cyclamate and saccharin reduced the bitter aftertaste of saccharin and offered many food processing advantages. This discovery led to the development of many cyclamate-containing foods.

REGULATORY HISTORY OF CYCLAMATE

After the FDCA was amended by the Food Additives amendment of 1958, cyclamate was reclassified as a GRAS substance (generally recognized as safe) and no specific limitations were defined for use in food products. However, cyclamate-containing products were required to bear labels indicating the foods should be used by those who should restrict their intake of calories.

During the 1960s, the intake of artificial sweeteners increased dramatically, corresponding with a growing weight consciousness by the public and the introduction of an array of low calorie products, particularly diet soft drinks. During the early 1960s the annual production of cyclamate increased nearly five-fold.

In 1962, the Food and Nutrition Board (FNB) of the National Academy of Science (NAS) undertook an evaluation of the status of cyclamate. In its final report, the FNB questioned the effectiveness of artificial sweeteners in aiding weight reduction and the safety of the sweeteners under conditions of widespread use. The FNB report did not appear to dampen public enthusiasm for artificial sweeteners but it did motivate further sweetener research.

Many artificial sweetener studies were conducted during the 1960s. While not all of these studies indicated deleterious effects from cyclamate, enough of them did to raise questions about the appropriateness of the GRAS status of cyclamate. On Dec. 5, 1968, FDA issued a memorandum that listed the following concerns about the safety of cyclamate: 1) cyclamate had been reported to alter intestinal function and cause stool softening; 2) cyclamate had been reported to damage the liver of guinea pigs, mice, and monkies; 3) cyclamate was reported to have the potential to alter the metabolism of certain therapeutic drugs and the absorption of vitamin K; and 4) some animal species were reported to convert a portion of the cyclamate consumed to cyclohexylamine (CHA), a toxic by-product.

FDA decided to remove cyclamate from the list of GRAS substances in October 1969 after scientific evidence suggested cyclamate may be a carcinogen. The pivotal study in this decision was sponsored by Abbott Laboratories and was conducted by the Food and Drug Research Laboratories (FDRL). In the FDRL study, rats were fed a 10 to 1 cyclamate to saccharin mixture, and some of the rats were also fed CHA. Of the 80 rats tested, 12 developed bladder tumors. This study did not conclusively establish cyclamate as the cause of the bladder tumors because saccharin was also present in the treatment mixture. Yet, because cyclamate was implicated as a possible carcinogen, it was removed from the GRAS list.

Department of Health, Education and Welfare (DHEW) Secretary Finch announced on Oct. 18, 1969 that cyclamate would be removed from the list of GRAS substances. He noted that while cyclamate had not been shown to cause cancer in humans, he was required by law to take a prudent course.

> ...Thus, my decision to remove cyclamates from the list of approved substances in no sense should be interpreted as a "lifesaving" or emergency measure. I have acted under the provisions of the law because it is imperative to follow a prudent course in all matters of public health.
>
> Specifically, the so-called Delaney amendment enacted 11 years ago states that any food additive must be removed from the market if it has been shown to cause cancer when fed to humans or animals.

While cyclamate was removed from the GRAS list under the general food safety provisions of the FDCA, and not under the Delaney clause, the clause appeared to influence the decision made by Secretary Finch.

Cyclamate was reclassified as an over-the-counter drug intended for use in the dietary management of diabetes and obesity [34 FR 17063]. The production of general purpose cyclamate-containing foods and beverages was stopped. Those cyclamate-containing products to be marketed as products bear labels stating, "For use only by diabetic or obese patients under medical supervision. Caution: medical supervision is essential for safe use."

However, the over-the-counter drug status of cyclamate lasted for less than one year, and cyclamate was banned outright on Aug. 27, 1970. The ban occurred when FDA concluded cyclamate did not meet the standard for "effectiveness" required for drugs according to the FDCA [35 FR 13644]. The ban complied with the advice of an HEW Medical Advisory Group. The Advisory Group believed that no substantial evidence existed indicating cyclamate compounds were effective at any level in the treatment of obesity or diabetes. In addition, the Advisory Group endorsed an outright ban of cyclamate because of concerns that it might not be safe, even when used with medical supervision.

CURRENT REGULATORY ISSUES

Critics of the cyclamate ban believe HEW acted without sufficient scientific evidence. Abbott Labs has sought approval of cyclamate as a food additive on two occasions since the ban. In November 1973, Abbott Labs submitted a food additive petition to FDA, citing new cyclamate studies [Food Additive Petition 4A 2975]. FDA announced its final decision denying approval of cyclamate in September 1980 because Abbott Labs had failed to establish the safety of cyclamate. FDA denied the petition on two grounds: 1) cyclamate had not been shown not to cause cancer; and 2) cyclamate had not been shown not to cause heritable damage. The final decision followed lengthy litigation before an administrative law judge.

Abbott Labs and the Calorie Control Council (CCC), an industry trade group, submitted a second food additive petition concerning cyclamate in November 1982. A decision on this petition is pending. FDA commissioned the NAS to reassess all relevant scientific data concerning the carcinogenicity of cyclamate in November 1983. The findings of this review were published in June 1985. The NAS report stated that the scientific evidence did not indicate cyclamate was by itself carcinogenic, but that some studies suggested it has cancer-promoting activity. The NAS review followed a 1984 FDA evaluation, conducted by the Center for Food Safety and Applied Nutrition, Cancer Assessment Committee, which reported there were

insufficient credible data to implicate cyclamate as a carcinogen. FDA is currently reviewing the NAS report and has stated that a final decision on cyclamate may be possible in 1986. Some groups have cautioned FDA against reapproving cyclamate without considering health risks other than the risk of cancer. Concern has been expressed about adverse effects such as reproductive abnormalities, atrophy of the testicles, and birth defects.

SACCHARIN

Saccharin is an artificial sweetener known chemically as "2,3 dihydro-3 oxobenzisulfonazole." By weight, saccharin is approximately 300 times as sweet as table sugar. The human body cannot use saccharin for energy so it is considered a "non-nutritive" sweetener.

Saccharin was first discovered in 1879 by a scientist at the Johns Hopkins University. The safety of saccharin was soon being scrutinized; that issue is still not fully resolved. The safety of saccharin has been evaluated by many different scientists including formal evaluations by scientific panels in 1911, 1955, and 1974. Each panel recommended maximum daily consumption levels for saccharin. Saccharin was banned once in 1912, but the ban was lifted during WWI when sugar supplies ran low.

REGULATORY HISTORY

On Mar. 9, 1977, the FDA proposed a saccharin ban again because research indicated it was an animal carcinogen. The pivotal study in FDA's decision was a "two generational" rat study conducted by scientists with the Health Protection Branch of the Canadian government. In this study, two successive generations of rats were fed high doses of saccharin. The second generation male rats developed cancerous and noncancerous bladder tumors. The study was considered significant because it demonstrated that saccharin caused bladder tumors. In previous studies it had been unclear whether saccharin or a saccharin impurity was responsible for producing tumors. Because the Delaney clause of the FDCA prohibits the marketing of food additives that cause cancer in man or animal, the Canadian study compelled FDA to propose the ban of saccharin.

In 1977, saccharin was the only artificial sweetener approved for use in the United States. Because of the popularity of artificially sweetened foods, particularly diet soft drinks, and the lack of a saccharin substitute, news of the proposed ban spawned a public outcry. The public response in turn motivated Congress to prevent FDA from banning saccharin, at least temporarily.

Congress intervened by passing the Saccharin Study and Labeling Act (P.L. 95-203), which was signed into law by President Carter on Nov. 23, 1977. This law is sometimes referred to as the "saccharin moratorium." The Act: 1) prohibited FDA from implementing the proposed ban of saccharin for 18 months; 2) required that within 90 days of enactment, all packages of saccharin and food containing saccharin would carry labels warning that the product may cause cancer; and 3) provided for a study of the toxicity and carcinogenicity of saccharin and its impurities, any health benefits associated with the use of non-nutritive sweeteners, and the evaluation of Federal regulatory policy.

An expert panel with the NAS carried out the study Congress requested in P.L. 95-203. In November 1978, the panel issued a report that assessed the risks associated with saccharin consumption. The panel stated that saccharin

was a carcinogen of relatively low potency but might be of moderate risk because of the large population exposed; and that no further studies were needed to establish the carcinogenicity of saccharin. In March 1979, the panel released a second report, which assessed U.S. food safety policy. The second report called on Congress to modify the policy in order to give FDA more discretion in regulating carcinogenic and other toxic substances in the food supply.

Over 170 saccharin studies have been published since 1977. Recent studies that have received particular attention were conducted by the International Research and Development Corporation (IRDC), the National Center for Toxicological Research (NCTR), and the National Cancer Institute (NCI).

THE INTERNATIONAL RESEARCH AND DEVELOPMENT CORPORATION (IRDC) STUDY

The IRDC study was sponsored by the Calorie Control Council and was carried out by the independent IRDC laboratory. Findings were released in 1983. The IRDC study was designed to define the dose response relationship between saccharin consumption and bladder tumor development in rats. Two successive generations of rats were fed diets ranging from 1% to 7.5% sodium saccharin, by weight. The study indicated that a dose reponse relationship existed between the amount of saccharin the rats consumed and the number of bladder tumors (cancerous and noncancerous) that developed in the second generation of rats. IRDC reported that the incidence of bladder tumors was especially marked when the diet was 4% saccharin or more. Furthermore, the study showed that the rats developed tumors even when they were not exposed to saccharin before birth. A limitation of the IRDC study is reportedly that too few rats were fed the 1% saccharin dose to determine with statistical significance if it could be considered a "no effect" level.

The IRDC study and other saccharin studies were reviewed by a panel of scientists convened by the Calorie Control Council. The panel reported that the IRDC findings indicated that the incidence of bladder tumors in the rats was especially marked at doses of 3% or more, and the effects of the 1% dose were equivocal. Based on the IRDC study and others, the panel concluded that the present level of human exposure to saccharin as a food additive is unlikely to present a cancer risk.

THE NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH (NCTR) STUDIES

A 1983 study conducted by the NCTR, an FDA laboratory, examined the tumor-promoting effects of saccharin in rats. The study was designed to determine if saccharin would increase the number of tumors, or the rate at which tumors were produced by another known carcinogen, N-methylnitrosurea (MNU). A low dose of MNU was applied directly to the bladders of the experimental rats. The rats were then fed saccharin doses ranging from one to five percent of diet, by weight. A dose reponse was reported that indicated that the greater the saccharin dose, the more quickly tumors were produced. A limitation of the NCTR study is said to be that the dose response was not consistent among rats receiving the highest saccharin dose (5% of diet). The investigators suggested this inconsistency probably occurred because the maximum tolerated saccharin dose for the rats was exceeded.

The response of mice to saccharin appears to differ from that of rats. In a NCTR study which examined the effect of saccharin on the promotion of liver tumors, saccharin was reported to inhibit tumor development. Whether human cells respond to saccharin more like rat or mouse cells is unclear. NCTR is

currently studying the response of human cells in culture. The findings of these studies are expected within two years.

THE NATIONAL CANCER INSTITUTE (NCI) STUDY

Many saccharin studies have been conducted in human populations to determine if artificial sweetener consumption increases human risk of bladder cancer. The impact of saccharin consumption alone is difficult to evaluate because cancer generally has a long latent period and, to study the appropriate time interval, data must be considered from years when saccharin and cyclamate were both marketed. The studies based on human populations (epidemiological studies) have not established an increased risk of bladder cancer for the general population using artificial sweeteners.

In 1979 NCI completed the largest epidemiological study ever conducted concerning artificial sweetener consumption and the risk of bladder cancer. NCI interviewed more than 3,000 bladder cancer patients and almost 6,000 people who did not have bladder cancer. The consumption of artificial sweeteners was compared across the groups. Seventy-five percent of the study participants were male and more than 50% were over the age of 67. Based on the interviews, NCI reported that in the general population artificial sweetener consumption was not associated with increased bladder cancer risk, but certain population segments may face increased risk. Increased risk was identified for the following three groups: 1) heavy users of artificial sweeteners (i.e., consume six or more servings, or 16 or more ounces of artificially sweetened beverages per day); 2) heavy smokers who were heavy consumers of artificial sweeteners had a greater risk of bladder cancer than heavy smokers who did not consume artificial sweeteners; and 3) those women who would normally be at low risk for bladder cancer but consumed artificial sweeteners two or more times daily had a greater risk of bladder cancer than similar women who never used artificial sweeteners.

There are said to be some limitations of the NCI study. Because the study results were based on interviews of participants, there is some uncertainty in accurately quantifying past artificial sweetener consumption. NCI noted that artificial sweetener consumption did not become widespread until most participants were well into adulthood. Therefore, the study was unable to assess the long-term impact of artificial sweetener consumption during pregnancy and childhood. In addition, NCI could not clearly distinguish between the effects of cyclamate and saccharin in this study because the sweeteners were marketed together in the same food products during the 1960s. Finally, some critics of the NCI study have not found the strength of the statistical evidence convincing that certain population subgroups experience a higher than average bladder cancer risk. In a preliminary report concerning the study, NCI noted that the possibility could not be excluded that the higher risk associations identified for certain subgroups represent chance variations.

CURRENT REGULATORY ISSUES

The Saccharin Study and Labeling Act has been amended three times to extend the moratorium on the proposed ban of saccharin. While the moratorium elapsed on Apr. 22, 1985, P.L. 99-46 was signed into law on May 25, 1985, which extended the moratorium again, until May 1, 1987.

An important argument used to support extensions of the moratorium in the past was the lack of another approved artificial sweetener. Aspartame was

approved for use in a number of dry food products in 1981. In July 1983 aspartame was also approved for use in carbonated beverages. Many manufacturers of artificially sweetened food products do not consider aspartame a complete substitute for saccharin because saccharin has certain food processing advantages (e.g., saccharin is more stable than aspartame in liquids and when heated). However, the approval of aspartame may erode support for extensions of the saccharin moratorium in the future if the approval of aspartame is further expanded.

ASPARTAME

Aspartame is an artificial sweetener synthesized from two amino acids, phenylalanine and aspartic acid. Amino acids are the chemical building blocks of protein. Because the human body can derive energy from the amino acids, aspartame is considered a "nutritive" sweetener. By weight, aspartame has about the same number of calories, and 200 times the sweetness, of table sugar. Therefore, aspartame can be used to sweeten foods and beverages at a smaller caloric cost than table sugar. Two teaspoons of sugar have 32 calories while the equivalent sweetening power of aspartame has about 0.4 calories.

Once consumed, aspartame is broken down to form the two constituents amino acid and methanol, substances that occur naturally in foods. Aspartame may also break down to form diketopiperazine (DKP) when added to liquids or exposed to acid or prolonged heat.

REGULATORY HISTORY

Aspartame was accidentally discovered in 1965 by a scientist with G.D. Searle and Company. Realizing the potential uses for the sweetener, Searle undertook extensive testing to establish the safety of aspartame. The company submitted its research findings to the FDA and sought approval of aspartame in March 1973. The studies indicated aspartame was safe for the general population, but Searle recommended it be avoided by individuals with phenylketonuria (PKU), a rare genetic disease. People afflicted with PKU must restrict consumption of the amino acid phenylalanine in order to prevent mental retardation. In July 1974, FDA approved Searle's food additive petition for aspartame. However, several formal objections were raised about the approval because of concerns that aspartame use by children might cause brain damage. In December 1975, FDA stayed the approval of aspartame until a comprehensive review of pertinent research could be completed. FDA reexamined the Searle research and concluded it was valid. In addition, FDA established a Public Board of Inquiry to clarify the evidence concerning aspartame consumption and brain damage. The Board concluded that aspartame consumption would not pose an increased risk of brain damage, but raised questions about its potential to cause brain tumors [48 FR 38286]. A subsequent study satisfied FDA that aspartame consumption also would not increase the risk of developing brain tumors.

On July 18, 1981, FDA commissioner Arthur Hull Hayes, Jr., ordered approval of aspartame for use in a number of dry food products. As a condition of approval, Searle was required to monitor the amount of aspartame actually used on the market. Also, the label of aspartame-containing products was required to state "Phenylketonurics: contains Phenylalanine." When marketed as a table-top sweetener, the product label was also required

to bear instructions indicating that aspartame should not be used in cooking because of its tendency to break down when exposed to prolonged heat [39 FR 27320].

Initially, aspartame was not approved for use in liquid products because it could break down more easily in liquids, losing sweetness and forming DKP, an undesireable by-product. However, on July 8, 1983, FDA amended the aspartame regulations to approve use in carbonated beverages and carbonated syrup bases. The expanded approval of aspartame occurred after Searle submitted evidence that satisfied FDA that: 1) the stability of aspartame in liquids was sufficient for the normal shelf-life of carbonated beverages, and 2) the increase in aspartame consumption resulting from approval would not have toxic effects. Searle currently markets aspartame under the trade name "Equal" as a table-top sweetener, and as "NutraSweet" when used as a sweetener added to foods during the manufacturing process.

CURRENT REGULATORY ISSUES

Aspartame has become a very popular artificial sweetener. It lacks the bitter aftertaste and the cancer warning associated with its only competitor, saccharin. Data suggest aspartame has not only attracted saccharin users, but individuals who previously did not use artificially sweetened foods. With the mounting popularity of aspartame, critics have grown increasingly concerned about the possible health effects of aspartame consumption.

Some critics are not convinced the safety of aspartame has been adequately established under the current conditions of use. The following list capsulizes some of the key concerns expressed by critics:

1) They suggest that the pivotal studies on which FDA based its initial approval of aspartame were conducted poorly and most were never replicated.

2) They suggest that some safety concerns were not adequately resolved, including whether aspartame may increase the risk of brain tumors, may interact with dietary carbohydrate and affect behavior, may interact with monosodium glutamate (MSG, a seasoning) and increase the risk of brain damage, whether the breakdown products of aspartame (phenylalanine, aspartic acid, methanol, DKP) may be harmful, and whether aspartame is safe at the levels now being consumed, and when marketed in liquids.

3) They suggest the regulatory process FDA followed before approving aspartame appeared to ignore systematically some of the safety concerns expressed by some FDA scientists and members of the Public Board of Inquiry. In addition, they suggest some scientists who favored the approval of aspartame in 1981 did so believing it would not be marketed in liquids because of the tendency of aspartame to break down in liquids.

Such concerns as those listed above prompted Senator Metzenbaum (OH) to request an investigation of the approval of aspartame by the General Accounting Office, in May 1985.

THE CENTERS FOR DISEASE CONTROL (CDC) AND FDA STUDY

Since aspartame was approved, FDA has received numerous health complaints which consumers believe are linked to the consumption of aspartame. In February 1984, CDC and FDA initiated an investigation of these complaints. The investigation was designed to determine if a pattern could be defined for the reported symptoms which would indicate a need for more detailed study. It was recognized at the outset that there were limitations in an investigation of already reported symptoms. The study would be unlikely to establish a cause and effect relationship between symptoms and aspartame consumption. Also, the investigation was probably more likely to detect rare and serious conditions occurring shortly after aspartame use, than symptoms common in the population and those occurring a long time after use.

CDC investigated 87% of the aspartame-related health complaints reported prior to mid-April 1984. CDC found that a variety of mild complaints had been reported that involved several organ systems. Symptoms included neurological symptoms such as headache, dizziness, and mood changes; gastrointestinal symptoms; allergic-type symptoms or skin reactions; and altered menstrual patterns. In November 1984, CDC concluded that the complaints did not provide evidence that serious, widespread, adverse consequences were attendant to the use of aspartame. Because of the limitations of the study, some people have recommended controlled clinical trials be conducted for aspartame in humans. In their final report, CDC noted that focused clinical trials would be the only way to evaluate whether some people have an unusual sensitivity to aspartame.

FDA has not changed its position concerning the safety of aspartame since it was approved in 1981 and 1983. The agency has maintained that aspartame is safe and is the most tested food additive in history. The FDA position is that all the health questions that have been raised so far have been adequately addressed. There are no plans to change the regulation of aspartame unless new research indicates a reevaluation is needed.

MULTIPLE SWEETENERS THEORY

At the Apr. 2, 1985 hearing on the saccharin moratorium, before the Senate Committee on Labor and Human Resources, FDA Commissioner Young stated he favored having more than one approved artificial sweetener on the market. He suggested multiple sweeteners offered public health advantages. Specifically, because there would not be heavy reliance on only one sweetener, the consumption of each sweetener would be reduced, thereby mitigating any potentially hazardous health effects.

The food processing industry may also benefit from having multiple approved sweeteners. Artificial sweeteners have different chemical properties making some more stable, better tasting, or more economical to use in different foods or beverages. In addition, some artificial sweetener mixtures have synergistic sweetening properties so that a smaller amount of two or more sweeteners can be used than if only one sweetener were used in a food. Industry may be able to develop a wider variety of artificially sweetened food products if there were a more versatile selection of sweeteners and sweetener combinations available.

The actual impact multiple sweeteners would have on public health is unknown. Whether or not consumers would in fact reduce their reliance on one sweetener is also unknown. Consumers are currently increasing their reliance

on aspartame despite the fact that both aspartame and saccharin are on the market. In addition, if the public continues to be weight-conscious, and if a wider variety of artificially sweetened food products become available, total artificial sweetener consumption could increase. The public health impact of increased exposures to many artificial sweeteners, or the nutritional impact of high artificial sweetener consumption in lieu of other dietary carbohydrates, is unclear.

Several artificial sweeteners are currently being tested and/or are in the regulatory pipeline at FDA. These include: acesulfame-K, thaumatin, Stevioside, Rebaudioside A, and L-sugars. In addition, FDA has not yet made a decision on the latest food additive petition concerning cyclamate. According to FDA, the approval of any of these sweeteners is not imminent.

SUMMARY

Artificial sweeteners continue to be a source of controversy. In general, the artificial sweetener issues center around the safety of each sweetener under the actual conditions of use by the public, the appropriateness of the food safety law under which the sweeteners are regulated, and whether the regulatory decisions made by FDA have been based on adequate or appropriate scientific evidence.

POINTS FOR FURTHER CONSIDERATION

Policymakers may wish to consider the following issues which have been raised concerning artificial sweeteners: 1) CYCLAMATE -- was the 1969 ban of cyclamate appropriate, and if not, should cyclamate be returned to the market? 2) SACCHARIN -- should the saccharin moratorium continue to be extended in light of the approval of aspartame? Are the saccharin warning labels currently used visible enough to comply with the intent of the Saccharin Study and Labeling Act? 3) ASPARTAME -- Did FDA adequately consider the potential health effects of aspartame consumption under the current conditions of use before it was approved? Are clinical studies needed to determine the effect of aspartame consumption on human brain metabolism and to determine if some people are sensitive to aspartame? Are label requirements needed to indicate the aspartame content of food products? 4) FOOD SAFETY -- Are the food safety laws appropriate and adequate to deal with the challenges of increasingly sophisticated analytical technology, and the uncertainties concerning public health effects of various food substances?

LEGISLATION

P.L. 99-46, S. 484

Amends the Saccharin Study and Labeling Act to extend to May 1, 1987, the period during which the Secretary of Health and Human Services may not take certain actions to restrict the continued use of saccharin or of any food, drug, or cosmetic containing saccharin. Introduced Feb. 2, 1985; referred to Committee on Labor and Human Resources; hearing held Apr. 2, 1985. The measure was reported to the Senate with an amendment to require aspartame content labeling on soft drinks, Apr. 22, 1985. The Senate passed the bill and rejected the amendment on May 5, 1985. The House passed S. 484 in lieu of H.R. 791 on May 14, 1985. President Reagan signed the bill into law on May 25, 1985.

H.R. 791 (Foley)

Amends the Saccharin Study and Labeling Act to extend the period during which the Secretary of Health and Human Services may not take certain actions to restrict the continued use of saccharin or of any food, drug, or cosmetic containing saccharin, Introduced Jan. 30, 1985; referred to Committee on Energy and Commerce, the Subcommittee on Health and the Environment.

HEARINGS

U.S. Congress. Senate. Committee on Labor and Human Resources. S. 484, a bill to extend the moratorium on the ban of saccharin for three years. Hearing, 99th Congress, 1st session. April 2, 1985. (not yet printed).

U.S. Congress. House. Committee on Interstate and Foreign Commerce. Subcommittee on Health and the Environment. Saccharin moratorium-bills to amend the authority of the Food and Drug Administration respecting the availability of saccharin, H.R. 4194, H.R. 1819, H.R. 4160, H.R. 4172 and all similar bills. Hearing, 96th Congress, 1st session. May 23, 1979. Washington, U.S. Govt. Print. Off., 1979. 176 p.

U.S. Congress. Senate. Committee on Labor and Human Resources. Subcommittee on Health and Scientific Research. The saccharin ban and food safety policy, 1979. Hearing, 96th Congress, 1st session. May 9, 1979. Washington, U.S. Govt. Print. Off., 1979. 323 p.

U.S. Congress. House. Committee on Interstate and Foreign Commerce. Subcommittee on Health and the Environment. Saccharin ban -- Oversight. Hearing on the findings of the National Academy of Sciences in the use of saccharin. Hearing, 96th Congress, 1st session. Apr. 11, 1979. Washington, U.S. Govt. Print. Off., 1979. 48 p.

U.S. Congress. House. Committee on Interstate and Foreign Commerce. Subcommittee on Health and the Environment. Moratorium on the saccharin ban. Hearing on H.R. 7753, directing the Institute of Medicine of the National Academy of Sciences to conduct a one-year review on the toxicity and carcinogenticity of food additives. Hearing, 95th Congress, 1st session. June 27, 1977. Washington, U.S. Govt. Print. Off., 1977. 143 p.

U.S. Congress. Senate. Committee on Human Resources. Subcommittee on Health and Scientific Research. The banning of saccharin, 1977. Hearing, 95th Congress, 1st session. June 7, 1977. Washington, U.S. Govt. Print. Off., 1977. 173 p.

U.S. Congress. House. Committee on Interstate and Foreign Commerce. Subcommittee on Health and the Environment. Proposed saccharin ban -- Oversight. Hearing, 95th Congress, 1st session. March 21 and 22, 1977. Washington, U.S.

Govt. Print. Off., 1977. 592 p.

U.S. Congress. Senate. Select Committee on Small Business. Food Additives: Competitive, regulatory and safety problems, parts and II. Hearings, 95th Congress, 1st session. January 13 and 14, 1977. Washington, U.S. Govt. Print. Off., 1977. 979 p.

U.S. Congress. House. Committee on the Judiciary. Subcommittee No. 2. Cyclamates. Hearings on H.R. 4264, H.R. 4180, H.R. 4265, H.R. 4870, H.R. 4912, H.R. 5848, H.R. 5862, H.R. 6163, H.R. 6155. Hearing, 92d Congress, 1st session. September 29 and 30; Octover 6, 1971. Washington, U.S. Govt. Print. Off., 1971. 384 p.

U.S. Congress. House. Committee on Government Operations. Cyclamate sweeteners. Hearings, 91st Congress, 2d session. June 10, 1970. Washington, U.S. Govt. Print. Off., 1970. 103 p.

REPORTS AND CONGRESSIONAL DOCUMENTS

U.S. Department of Health, Education and Welfare. National Institutes of Health. Report of the Temporary Committee for the Review of Data on Carcinogenicity of Cyclamate. Bethesda, Maryland. February 1976.

U.S. Congress. House. Committee on Appropriations. Study of the Delaney clause and other anticancer clauses. Hearings, 93rd Congress, 2d session. May 6, 1974, part 8. Washington, U.S. Govt. Print. Off., 180 p.

U.S. Congress. House. Committee on Government Operations. Regulation of cyclamate sweeteners. Thirty-sixth report. Washington, 1970. 17 p. (91st Congress, 2d session. House. Report no. 91-1585).

U.S. Congress. House. Committee on Interstate and Foreign Commerce. Saccharin extension (H.R. 4453). Washington, 1979. 55 p. (96th Congress, 1st session. House. Report no. 96-348).

U.S. Congress. House. Committee on the Judiciary. Compensation for losses resulting from the ban on cyclamates (H.R. 13366). Washington, 1971. 19 p. (92d Congress, 2d session. House. Report no. 92-1070).

U.S. Congress. Senate. Committee on Agriculture, Nutrition and Forestry. Food safety: where are we? Washington, 1979. (96th Congress, 1st session. comm. print) 678 p.

U.S. Congress. Senate. Committee on Commerce, Science, and Transportation. Saccharin Study, and Labeling and Advertising Act (S. 1750). Washington, 1977. 7 p. (95th Congress, 1st session, Senate, Report no. 95-369).

U.S. Congress. Senate. Commtee on Human Resources. Amending the Public Health Service Act (S. 1750). Washington, 1977. 22 p. (95th Congress, 1st session. Senate. Report no. 95-353).

CHRONOLOGY OF EVENTS

05/25/85 -- President Reagan signed S. 484 (P.L. 99-46) extending the saccharin moratorium until May 1, 1987.

05/23/85 -- Senator Metzenbaum requested a GAO investigation of the approval of aspartame.

05/14/85 -- The House passed S. 484 in lieu of H.R. 791.

05/07/85 -- The Senate passed S. 484.

04/02/85 -- The Senate Committee on Labor and Human Resources held a hearing on S. 484, a bill to extend the saccharin moratorium; and to review the status of cyclamate and aspartame.

12/00/84 -- In the lawsuit between the California Canners and Growers Association and the U.S., a hearing officer recommended the Association be awarded 6.4 million dollars for damages arising out of erroneous government publicity issued in connection with the removal of cyclamates from the market.

07/00/84 -- The National Academy of Sciences, at the request of FDA, initiated a review of the scientific evidence concerning the carcinogenicity of cyclamate.

06/00/84 -- The FDA's Center for Food Safety and Applied Nutrition, Cancer Assessment Committee issued a report which concluded there was insufficient credible data to implicate cyclamate as a carcinogen in the laboratory animals tested.

03/00/84 -- The FDA and Centers for Disease Control (CDC) initiated a study of consumer complaints concerning aspartame.

07/08/83 -- FDA approved the use of aspartame in carbonated beverages and carbonated syrup bases.

04/22/83 -- P.L. 98-22 (S. 89) was signed into law, extending the saccharin moratorium until April 22, 1985.

11/12/82 -- Abbott Laboratories and the Calorie Control Council filed the second petition for cyclamate use as a food additive since the ban of cyclamate in 1969.

07/24/81 -- FDA approved aspartame for use in certain dry food products.

10/00/80 -- FDA Public Board of Inquiry issued a report concerning aspartame safety.

09/16/80 -- FDA announced the final decision which denied the food additive petition for cyclamate submitted by Abbott

Laboratories.

06/17/80 -- P.L. 96-273 was signed into law which extended the saccharin moratorium until June 30, 1981.

02/04/80 -- An FDA Administrative Law Judge issued the second Initial Decision on the cyclamate food additive petition which said the petitioner, Abbott Laboratories, had failed to establish the safety of cyclamate. This decision followed a review of further hearing evidence which had been requested by the Commissioner of FDA.

12/20/79 -- The preliminary findings of the National Cancer Institute study on human bladder cancer were announced by FDA. The findings indicated artificial sweetener consumption did not increase the risk of bladder cancer in the general population, but may increase the risk in certain population subgroups as much as 50 percent.

05/23/79 -- The House Committee on Interstate and Foreign Commerce, Subcommittee on Health and the Environment held a hearing on the saccharin moratorium.

05/09/70 -- The Senate Committee on Labor and Human Resources, Subcommittee on Health and Scientific Research held a hearing on the proposed ban of saccharin and food safety policy.

04/11/79 -- The House Committee on Interstate and Foreign Commerce, Subcommittee on Health and the Environment held an oversight hearing concerning the proposed ban of saccharin and the findings of the NAS concerning the carcinogenicity of saccharin.

03/02/79 -- The NAS released the findings of the food safety policy study, which was mandated under the Saccharin Study and Labeling Act in 1977. In the report, NAS called for major changes in existing food safety laws.

12/00/78 -- FDA confirmed the validity of the aspartame studies conducted by Searle.

08/04/78 -- An FDA Administrative Law Judge issued an Initial Decision on the food additive petition concerning cyclamate, and concluded the petitioner, Abbott Laboratories, had not established the safety of cyclamate.

01/25/78 -- The FDA and National Cancer Institute announced a major study designed to determine if artificial sweetener consumption increases the risk of bladder cancer in humans.

11/23/77 -- P.L. 95-203, The Saccharin Study and Labeling Act was signed into law. The law required a moratorium

on the proposed ban of saccharin, product labeling, and a NAS review of saccharin research studies and food safety policy.

06/27/77 -- The House Committee on Energy and Commerce, Subcommittee on Health and the Environment held a hearing on a bill concerning a saccharin moratorium, and on recent saccharin studies.

06/07/77 -- The Senate Committee on Human Resources, Subcommittee on Health and Scientific Research held a hearing to evaluate the scientific basis for the ban of saccharin proposed by FDA.

05/18/77 and 05/19/77 -- The FDA held public hearings on the proposed ban of saccharin.

04/20/77 -- A formal evidentiary hearing was held before an FDA Administrative Law Judge concerning the food additive petition for cyclamate submitted by Abbott Labs.

04/15/77 -- FDA published the proposed ban of saccharin in the Federal Register. The regulations would revoke the interim food additive regulation and would permit marketing of saccharin as a single-ingredient drug.

03/24/77 -- The Senate Committee on Human Resources, Subcommittee on Health and Scientific Research held a hearing to consider the proposed ban of saccharin.

03/21/77 and 03/22/77 -- The House Committee on Interstate and Foreign Commerce, Subcommittee on Health and the Environment held a hearing on the proposed ban of saccharin.

03/09/77 -- FDA announced plans to ban saccharin in foods and beverages because of the findings of the Canadian study which indicated saccharin may be a human carcinogen.

01/13/77 and 01/14/77 -- The Senate Select Committee on Small Business held a hearing concerning the competitive, regulatory and safety problems associated with food additives.

10/04/76 -- Abbott Labs. and the Calorie Control Council filed a formal objection to FDAs denial of the cyclamate food additive petition and requested a formal evidentiary hearing.

12/00/75 -- FDA stayed regulations which would have permitted marketing of aspartame.

12/00/74 -- The NAS recommended that more research be done on the carcinogenicity of saccharin, based on the findings of a review of saccharin studies which was conducted at the request of FDA.

10/04/76 -- The denial of the food additive petition concerning cyclamate, submitted by Abbott Labs. was published in the Federal Register.

02/00/76 -- The Temporary Committee for the Review of Data on the Carcinogenicity of Cyclamate of the National Institutes of Health issued their final report. The report stated that the evidence did not establish the carcinogenicity of cyclamate or its principle metabolite, cyclohexylamine, in experimental animals.

07/00/74 -- FDA approved aspartame for use as a food additive.

11/15/73 -- Abbott Labs. filed a food additive petition requesting FDA approval of cyclamate as a sweetening agent in food.

03/00/73 -- Searle filed a food additive petition requesting approval of aspartame as a sweetening agent in food.

09/07/72 and 09/08/72 -- The Senate Committee on the Judiciary, Ad Hoc Subcommittee held a hearing on cyclamate.

09/29/71 and 09/30/71 and 10/06/71 -- The House Committee on the Judiciary, Subcommittee No. 2 held a hearing on several bills regarding cyclamate.

08/27/70 -- FDA published regulations in the Federal Register which banned all uses of cyclamate.

06/10/70 -- The House Committee on Government Operations held a hearing on cyclamate sweeteners.

10/18/69 -- FDA announced cyclamate would be removed from the list of GRAS substances because of research which suggested cyclamate may cause bladder cancer in test animals.

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U.S. Library of Congress. Congressional Research Service. Perspectives on current food safety policy: proceedings of a Congressional Research Service Service seminar (by) Donna V. Porter. August 1981. Multilith 81-215. 84 p.

APPENDIX 1
REGULATORY STATUS OF SACCHARIN, CYCLAMATE, AND ASPARTAME IN EUROPE AS OF APRIL 24, 1983

AUSTRIA (sacch.-TFB; cycl.-T; aspart.-T)

BELGIUM (sacch.-TFB; cycl.-T; aspart.-T)

DENMARK (sacch.-TFB; cycl.-T; aspart.-TFB)

FINLAND (sacch.-TFB; cycl.-TB)

FRANCE (sacch.-T; cycl.-T; aspart.-T)

LUXEMBOURG (sacch.-TFB; cycl.-T; aspart.-T)

NETHERLANDS (sacch.-TFB; cycl.-TB)

NORWAY (sacch.-TFB; cycl.-TFB; aspart.-T)

PORTUGAL (sacch.-T; cycl.-T)

SPAIN (sacch.-TFB; cycl.-TFB)

GREAT BRITAIN (sacch.-TFB)

GREECE (sacch.-T)

IRELAND (sacch.-TFB; cycl.-TB; aspart. TFB)

ITALY (sacch.-TFB; cycl.TFB)

SWEDEN (sacch.-TB; cycl.-T; aspart.-TFB)

SWITZERLAND (sacch.-TFB; cycl.-TFB; aspart.-TFB)

WEST GERMANY (sacch.-TFB; cycl.-TFB; aspart.-T)

SYMBOLS: "T" = Approved as table top sweetener "F" = Approved as ingredient in foods "B" = Approved as ingredient in beverages

SOURCE: INTERNATIONAL SWEETENERS ASSOCIATION, PO BOX 768,CH-8026 ZURICH, SWITZERLAND

APPENDIX 2

PER CAPITA CONSUMPTION OF ARTIFICIAL SWEETENERS, 1963-83

[KEY: pounds of sweetener consumed compared to the pounds of sugar needed to achieve the same sweetness* (in parenthesis).

YEAR	CYCLAMATE	SACCHARIN	ASPARTAME
1963	.023 (0.7)	.010 (3.0)	0
1964	.043 (1.3)	.012 (3.5)	0
1965	.056 (1.7)	.013 (4.0)	0
1966	.063 (1.9)	.015 (4.5)	0
1967	.070 (2.1)	.016 (4.8)	0
1968	.073 (2.2)	.017 (5.0)	0
1969	.050 (1.6)	.018 (5.3)	0
1970	**	.019 (5.8)	0
1971	**	.017 (5.1)	0
1972	**	.017 (5.1)	0
1973	**	.017 (5.1)	0
1974	**	.019 (5.9)	0
1975	**	.020 (6.2)	0
1976	**	.020 (6.1)	0
1977	**	.022 (6.6)	0
1978	**	.023 (6.9)	0
1979	**	.023 (7.0)	0
1980	**	.024 (7.1)	0
1981	**	.024 (7.2)	.001 (0.2)
1982	**	.024 (7.3)	.005 (1.0)

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*/ The sweetness factors used to calculate the pounds of sugar are assumed to be: Cyclamate, 30 times the sweetness of sugar; Saccharin, 300 times the sweetness of sugar; and Aspartame, 200 times the sweetness of sugar.

**/ Cyclamate was removed from the GRAS list in October 1969, and was banned in August 1970.

Source: Adapted from USDA Economic Research Service consumption data.