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ALTERNATIVE SWEETENERS

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Saccharin is the only non-nutritive sweetener currently available to the American people. Other artificial sweeteners, however, have been used at other times and in other countries. Still other alternatives are currently under investigation. Sorbitol, xylitol, and mannitol are nutritive sweeteners. Non-nutritive sweeteners whose names have been occasionally mentioned in the literature include stevioside, osladin, d-6 chlorotryptophan, and SRI-oxime V. Six other non-nutritive sweeteners—cyclamate, aspartame, neohesperidan dihydrochalcone, miraculin, monellin, and thaumatin I and II—have been discussed in the literature more extensively. This review is limited to these six.

Various problems make it unlikely that any of these substances, with the possible exception of cyclamate, will be approved for marketing in the immediate future.

- Cyclamate, aspartame, and neohesperidan will not be considered for approval until the necessary toxicity data are submitted and reviewed.
- Aspartame, while stable in dry form, is unstable in alkaline solutions, and the activity of the sweetener declines with storage. Primary use of aspartame would be in dry products.
- Miraculin, monellin, and thaumatin I and II were all isolated from fruits native to tropical West Africa. It would be necessary to produce these fruits in the United States in order for mass marketing of the sweetener to be economically feasible.
- Neohesperidan dihydrochalcone is characterized by a sweet sensation that is slow in onset, long in duration, and accompanied by an aftertaste similar to licorice or menthol.
- Monellin is characterized by a lingering sweetness.
- Thaumatin I and II are unstable at high temperatures as well as having a licorice aftertaste.

Other salient characteristics of these non-nutritive sweeteners and saccharin are summarized in table 3.

CYCLAMATE

Cyclamate was introduced into the market in 1950 and placed on the generally recognized as safe (GRAS) list in 1959. In 1970, however, FDA banned the use of cyclamates in all foods and drugs. This action was taken because experiments on the chronic toxicity and metabolism of a combination of cyclamate and saccharin resulted in bladder tumors in the rats tested (76,1 18). In addition, cyclohexylamine, a

Table 2 — Salient Characteristics of Non-Nutritive Sweeteners

Sweetener	Origin	Relative Sweetness to Sucrose	Taste Characteristics	Stability	Use
Cyclamate	hexane sulfonic acid	30-180	no aftertaste	stable	dry products beverages foods
Aspartame	methyl ester of dipeptide, L-aspartyl-L-phenylalanine	160-220	no aftertaste	stable in dry form; unstable in alkaline solutions and at prolonged cooking temperatures; decline of activity with storage	table use cold breakfast cereals chewing gum dry bases for: beverages instant coffee, tea gelatins puddings fillings dairy product
Neohesperidin dihydrochalcone	conversion of: neohesperidin in Seville orange C. aurantium — naringin in grapefruit C. paradisi — hesperidin in C. sinensis	1,000-2,000	slow in onset long in duration aftertaste similar to menthol or licorice		
Maltol	maltololone, Symplocos denticulata		very sweet long in duration (1 to 2 hrs) quality of sweetness — "good"		chewing gum candies dessert puddings fruit-flavored drink mixes
Monellin	serendipity berry, Dioscoreophyllum cumminsii Diels	800-1,500	long in duration (1 or more hrs)	stable	
Thaumatin I, II	katemfe fruit, Thaumatococcus daniiellii Benth	1,600	long in duration bitter aftertaste	unstable at high temperature	previous use: bread fruits wine tea
Saccharin	synthetic	200-700	bitter aftertaste	stable at room temperature heat labile	dry products beverages foods

metabolize of cyclamate, reportedly has caused not only chromosomal abnormalities and testicular atrophy in test animals, but also dermatitis and convulsions in humans, when inhaled or applied to the skin (76,136).

Many long-term studies of cyclamate's carcinogenicity and cocarcinogenicity have been conducted in laboratory animals since the removal of cyclamates from the market. All have been negative. Studies of cyclohexylamine, however, have not been conclusive.

In light of these additional tests, Abbott, one of the original manufacturers of cyclamate, petitioned FDA in November 1973, to permit the use of the sweetener in specific dietary foods. In September 1974, FDA asked Abbott to withdraw its petition until data could be provided on the safety of the product. On April 20, 1977, a preheating conference was held to establish a schedule for disclosure and submission of documentary materials. A hearing on cyclamate began on July 13, 1977.

ASPARTAME

In March 1973, G.D. Searle and Company filed a petition for aspartame, a white crystalline powder intended for use as a tabletop sweetener. FDA approved aspartame as a food additive for a number of foods in July 1974, Objections to the regulations were filed, and FDA announced its intention to convene a Public Board of Inquiry. Prior to the establishment of the Board, however, an investigation of the records from animal studies indicated the need for a comprehensive review of some of the data. The Public Board of Inquiry was postponed, and in December 1975, the regulation to permit the use of aspartame was stayed (16).

Objections to aspartame centered on the potential risk of brain damage, primarily in infants and children (57). It has been suggested that large doses of aspartame or combinations of aspartame and monosodium glutamate could cause brain damage in young children. Young mice in one study have developed brain damage similar to that caused by glutamate and aspartame when administered aspartame by feeding tube (118). It has also been reported that lesions were produced in the hypothalamus after aspartic acid and glutamic acid were administered in very large single doses to newborn rodents (118).

Elevated levels of phenylalanine, an amino acid present in aspartame, are associated with the development of mental retardation. Ingestion of aspartame may be harmful to those individuals with phenylketonuria (PKU), a disease characterized by the inability to degrade phenylalanine. The relationship between ingestion of aspartame and metabolism of phenylalanine has been the subject of several studies. A study of 45 adults, all parents of known PKU patients, found acceptable levels of serum phenylalanine among subjects who used aspartame over a 28-week period (83). A study of 126 children and adolescents found that aspartame, when used over a 13-week period, had no significant effect on plasma levels of phenylalanine (52).

Aspartame may not be marketed until the review is completed and all questions raised about its safety resolved.

NEOHESPERIDAN DIHYDROCHALCONE

FDA has recently received petitions from two manufacturers asking for approval of neohesperidan dihydrochalcone, a product derived from bitter citrus flavanones (substances present in the rind of grapefruits and sweet oranges). In August 1975, Neutrality Products, Inc., submitted a second petition—the first having been withdrawn when necessary toxicology tests were requested—for the use of the sweetener in mouthwash, toothpaste, and chewing gum. That petition is still incomplete, pending receipt of the toxicology data.

In March 1977, California Aromatics and Flavors, Inc., a Division of Research Organic/Inorganic Chemical Company, asked for approval of the use of neohesperidan dihydrochalcone as a sweetener. Until the use for the sweetener is specified by the manufacturer and the necessary toxicology tests are identified by FDA, no action may be taken toward the approval of its petition.

Although FDA might approve these petitions, the taste characteristics of neohesperidan dihydrochalcone could discourage widespread use. Its sweet sensation is slow in onset, usually long in duration, and accompanied by a slight licorice after-taste.

MIRACULIN

Miraculin is a glycoprotein found in the berries of the Nigerian fruit, *Synsepalum dulcificum*. These berries are commonly eaten by children in West Africa. "Miracle fruit" was first described in the literature in 1852. It is a taste modifier that causes sour foods to taste sweet. The sweet sensation is long lasting—often up to 2 hours.

The Miralin Corporation began test marketing miracle fruit as a GRAS food item in 1973. In September 1974, a petition was filed to affirm GRAS status of the fruit for use in foods as a sweetening agent or flavor enhancer. After a preliminary evaluation, however, the petition was denied because the information on consumption in the United States and in existing scientific studies to support the GRAS determination was found to be inadequate. The data were also considered insufficient for the issuance of a food additive regulation at that time. The product was immediately removed from the market.

In May 1977, the FDA announced that it will not permit the *marketing* of "miracle fruit" because its safety for long-term use has not been demonstrated.

MONELLIN

Monellin is a sweetener isolated from the fruit of the West African plant, *Dioscoreophyllum cumminii* Diels. The fruit is often referred to as the "serendipity berry." Research is being conducted on the reasons for monellin's sweet taste. The commercial possibilities for marketing the sweetener are not being investigated at this time.

No petitions for affirmation of GRAS status or food additive classification have been filed with the FDA.

THAUMATIN I, II

In 1972, two proteins, Thaumatin I and II, were extracted from the Nigerian fruit, *Thaumatococcus danielli* Benth. The seeds from the fruit have been used in West Africa since 1839 to sweeten bread, fruits and wine. The interest in thaumatin, like that in monellin, centers on the reasons for its sweet taste.

No petitions for affirmation of GRAS status or food additive classification have been filed with the FDA.