Food Additives and Contaminants

An Update

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Food additives continue to be a source of benefits to the consuming public but there are also perceived risks. Concern for the latter in the last decade has produced a society afflicted with cancer phobia. The intentional additives including sugars, salt, corn syrup, and dextrose make up 90% of the direct additives. These, along with a limited number of familiar items make up a large proportion of the remainder of the additives. Such common ingredients as nitrates and nitrites, solanine, cyanogenetic compounds, arsenic, *etc.*, are unavoidably consumed in the diet and with little if any evidence for public health consequences. Major concern on the part of the public in recent years has been focused on man-made chemicals which are intentionally added to foods to enhance flavors and acceptability, nutrient value, shelf life and increased availability. These include food colors, nonnutritive and low-nutrient sweeteners, (saccharin, cyclamate, aspartame); antioxidants; and nitrities. Contaminants, sometimes incorrectly included in lists of food additives, present the greatest potential threat to public health. Such contaminants as mycotoxins, nitrosamines, polychlorinated biphenyls (PCBs), pesticides, among others, provide a continuing challenge to our regulatory agencies and to public health authorities. Evidence to date indicate that these responsible for food safety are doing an admirable job, and as a society, our food supply has never been better, or safer, and, as a population, we have never been healthier. Aside from contaminants, major concerns relate to an excess of good food and to obesity. These comments should not be taken to infer that we should relax our concern and surviellance; instead more concern and surviellance should be exerted toward those uncontrolled substances such as natural plant products and alleged natural nutrients, roots, herbs, *etc.*, which are given much credit for positive health effects, without meeting the high standards of our legitimate food industry.

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A GROWING CONCERN and confusion about the safety of food additives and chemicals in our environment has emerged over the last two decades. We have been mesmerized by neoplasia (cancer) and, as a society, we have developed what has been described as a national cancer phobia. These events have led to numerous reviews of safety for existing substances, testing of old and new substances and formulation of new and ostensibly better controls on safety evaluation, risk assessment and risk management. The National Toxicology Testing Program, (NTP) a descendant of the original National Cancer Institute's carcinogenesis testing program, was implemented to provide more adequate information and control over materials to which the public is exposed. Numerous guidelines have been established by many different agencies within the government and an Interagency Regulatory Liaison Group (IRLG) was established[1] several years ago, which included the Consumer Product Safety Commission (CPSC), the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the Occupational Safety and Health Administration (OSHA).

This was an original draft and has long since been superceded by additional, more formalized recommendations. The FDA also has promulgated Good Laboratory Practices (GLP), regulations prescribing explicitly the conduct, monitoring, recording and reporting of animal studies, beginning in 1978.[2] Other food regulations have been added to the legal arm of the FDA over the past many years, reviewed in detail by Hutt.[3]

Thus there has been a continuum since the early days of our government to attempt to provide for the safety of foods in an ever increasing comprehensive manner. Despite the efforts of the various agencies, the public in recent years has developed a growing skepticism about the va-

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TABLE 1. Direct Food Additives Accounting for 93% of Total US Consumption per Capita (Pounds)

Sugar (sucrose)	100
Table salt (sodium chloride)	15
Corn syrup	8
Dextrose	4

From Larkin.[6]

lidity of animal tests that are used as the basis for determining the safety of food and food additives. There has been a tendency to believe that regardless of the scientific basis for and interpretation of data, testing programs will reveal "a new carcinogen of the week, reported on a continuing basis." This is particularly the case when common foods and beverages that have been consumed for eons of time and come under attack. The proposed banning of saccharin led to such a public rebellion that Congress interceded to delay any regulatory action; that intervention is still in effect renewed in May 1985 allowing saccharin to be consumed by the public in general.

Corresponding to the broad definition of food additive use in this report is the technical definition of the Food Protection Committee of the Food and Nutrition Board, National Academy of Sciences. This definition states that a food additive is "a substance or mixture of substances other than the basic foodstuff which is present in a food as a result of any aspect of production, processing, storage or packaging." Thus, a food additive may be a substance intentionally incorporated into a product or a substance that becomes a component of food as a consequence of its journey from the field to the family dinner table. The former, intentional additives, are referred to as direct additives and are there to serve some functional purpose in the food such as adding or enhancing flavor, sweetness, or color, or to prevent spoilage. The latter are called indirect additives and are normally present only in trace amounts resulting from contact of the food with agricultural chemicals, with processing equipment or processing aids, or from contact with the food container.

Popular discussion of food additives usually focuses on a very few items such as the food colors, sweetners, (cyclamate, saccharin, and aspartame); preservatives, (sodium nitrite), and more recently, synthetic antioxidants such as butylated hydroxyanisole (BHA) and butylated hydroxytolulene (BHT). In some cases container materials

TABLE 2. Familiar Items Accounting Collectively for the Consumption of About Three Pounds Annually per Individual

Modified starch	Caramel
Yellow mustard	Citric acid
Sodium bicarbonate	Carbon dioxide
Yeasts	Black pepper

From Hall.[7]

such as polyvinyl chloride and others also have come under scrutiny, although the number is limited. This tendency to focus on a few substances is characteristic even though there are literally thousands of food additives, the exact number depending on whether only officially recognized additives are included and on how detailed a breakdown there may be. The National Science Foundation[4] refers to 1850 officially recognized substances added to foods for specific technical effects. The FDA on the other hand lists about 2800 direct additives.[5] The vast majority of the direct additives are spices and flavors including such familiar items as salt, pepper, sugar, mustard, and yeast.

Whereas no one really knows how many indirect additives there are, the National Science Foundation has noted the existence of nearly 3000 additives permitted for use in food packaging materials. The FDA, on the other hand, has estimated that there is probably in excess of 10,000 indirect additives. Despite these rather large numbers only a small fraction become additives in the sense that they actually end up in food. It has been pointed out[6] that four familiar food ingredients account for about 93% by weight of all the direct food additives used in the United States. These are sugar (sucrose), salt, corn syrup, and dextrose. On a per capita basis the annual use in 1970 of sucrose was about 100 pounds, salt about 15 pounds, corn syrup about 8 pounds and dextrose about 4 pounds. These are listed in Table 1. All of the remaining direct additives together are used at the rate of somewhat less than 10 pounds annually per individual. If one includes the familiar items listed in Table 2, which collectively account for about 3 pounds/person annually, 95% of direct additive consumption is covered.[7]

Of the direct additives other than the big four shown in Table 1 90% of the 10 pounds/person consumed annually are accounted for by the following: (1) stabilizers/thickeners (sodium caseinate, gum arabic, and modified starch); (2) flavors and flavor enhancers, (hydrolyzed vegetable protein, black pepper, mustard, monosodium glutamate); (3) leavening agents, (sodium acid phosphate, sodium aluminum phosphate, monocalcium phosphate, yeasts); (4) leavening/acidity control, (sodium carbonate, calcium carbonate, dicalcium phosphate, disodium phosphate); (5) acidity control, (sodium bicarbonate, citric acid, sulfuric acid, sodium citrate, hydrogen chloride, sodium hydroxide, acidic acid, phosphoric acid, calcium oxide); (6) emulsifiers, (monoglycerides, tryglycerides, lecithin); and (7) miscellaneous, (sulfur dioxide preservative, calcium chloride, firming agent, calcium sulfate, processing aid, carbon dioxide effervescent, sodium tripolyphosphate, curing humectant and caramel color).[7] Thus, other than the big four additives the total consumed at the annual rate of 10 pounds/person gives an average use of 0.08 of an ounce or about 2.25 g for each of the additives other

than the big four. The vast majority however are used at much smaller levels than the average, the medium per capita being about 0.5 mg. This means that 50% of the additives are used at the annual per capita rate of 0.5 mg or less, about the weight of a grain of table salt. It has thus been estimated that about 0.5% of our food supply consists of intentional additives. These figures then provide a reasonable approximation of the intentional exposure of humans to direct food additives.

It is not possible to accurately estimate human exposure to indirect additives but a few comments at this point may place the matter in perspective. The average American consumes about 120 pounds of potatoes per year; contained in these potatoes are around 10 g of the toxic alkaloid solanine, a margin of 20,000 over the 0.5 mg of direct food additives. In addition, lima beans, which are consumed at a level of about 0.5 pounds annually results in the ingestion of about 40 mg of hydrogen cyanide, a highly potent, acute toxin. We also ingest about 14 mg of arsenic annually from seafoods. Nitrate and nitrites are consumed in very large quantities and these are known toxic indirect food contaminants, although at the amounts consumed normally, they are safe. Celery, radishes, beets, and leafy vegetables are rich sources of nitrates, some samples containing up to 15,000 ppm. Nitrates are converted to nitrites by bacteria in the oral cavity and the gastrointestinal tract. Nitrites from ingested foods, other than cured meats, amount to about 8 to 10 mg/day compared to 1 to 2 mg/day from cured meats.[8,9]

Thus from the limited examples noted above, it is clear that the human population consumes, and sustains, the effects of large amounts of toxic materials in their daily food supply.[10] A much more comprehensive and detailed view of this can be gained from a review of the National Academy of Sciences Publication, *Toxicants Occurring Naturally in Foods.*[11]

In addition, a few of the more common but significant direct food additives which have become of public concern in recent years need to be considered. The food ingredients added directly and regulated by the FDA, aside from Generally Regarded as Safe (GRAS) substances and color additives, are listed in part 172 of the Code of Federal Regulations entitled, *Food Additives Permitted for Direct Addition to Food for Human Consumption.* This list can be referred to for further information.

Colors

Color additives are officially designated as either subject to or exempt from certification. Under certified colors, surprisingly, there are relatively few synthetic color additives approved for use in the United States but these are important to the food and cosmetic industries. Noncertified, natural colors, in contrast to certified colors, have caused very little safety concern probably because of the popular belief that "natural is good." Currently, however regulatory scrutiny is beginning to focus on food and color additives derived from natural sources. The FDA recognized by regulation 22 color additives exempt from certification. These are shown in Table 3, along with some which have been banned in recent years.

TABLE 3. Food Color Additives

Exempt from Certification	
Dried algae meal	Canthaxathin
Annatto extract	Caramel
Beet powder	Carrot oil
Beta apo 8-carotenol	Cochineal extract
Beta-carotene	Corn endosperm oil
Toasted cottonseed flour	Paprika oleo resin
Ferrus gluconate grapeskin extract	Riboflavin
Synthetic iron oxide	Saffron
Fruit juice	Thetes meal and extract
Vegetable juice	Titanium dioxide
Paprika	Tumeric oleo resin
Prohibited from further use	
FD&C red no. 1	FD&C violet no. 1
FD&C red no. 2	FD&C yellow no. 2
FD&C red no. 4	FD&C yellow no. 3
FD&C green no. 2	Orange no. 1

Adapted from Roberts.[12]

Of all of these recognized as exempt, caramel is the most widely used food color and has been considered "generally regarded as safe" (GRAS). There are three types of caramel colors, not elaborated on here, but each of them serve different purposes. These colors have been used in a variety of foods for more than a 100 years. Toxicity studies conducted over the last 20 years in both rodent and nonrodent species indicate the safety of caramel but this was called into question when studies in rats suggested that some of the colors might cause problems. These questions however have been resolved. Thus, today caramels are freely and widely used in foods and in beverages.

In 1977 the FDA published in the Federal Register regulations that required new chronic toxicity studies on 31 color additives.[12] The FDA required that these new chronic studies be conducted because the older studies submitted in support of listing the color additives were deficient with respect to contemporary scientific standards. Along with these requirements the FDA extended the provisional listing of these color additives from January 1981 for the completion of the studies and the evaluation of results.

The companies supplying the colors attempted to meet these requirements but a number of problems arose with the animal testing systems and the FDA was petitioned to extend the period of time allowed for testing. The FDA adopted the final rule that granted the request of the extension for 23 of the color additives. This allowed the agency time to evaluate the studies that were to be com-

TABLE 4. Colors Now Under Study, Due Time of Final Report

FD&C red no. 3	September 3, 1986
FD&C yellow no. 6	June 6, 1986
D&C red no. 8	June 6, 1986
D&C red no. 9	June 6, 1986
D&C red no. 19	June 6, 1986
D&C red no. 33	September 3, 1990
D&C red no. 36	September 3, 1990
D&C red no. 37	June 6, 1986
D&C orange no. 17	June 6, 1986
FD&C yellow no. 5	September 3, 1985
FD&C blue no. 2	At time of final decision on permanent listing

From Federal Register.[13]

pleted by the industrial concerns promoting the color additives. The data from studies of nine of the color additives raise questions about some of them. The closing date for the provisional listing was September 3, 1985.

The issues presented by the uses of the color additives are complex and a number of new questions have been raised that test the capacity of modern toxicological sciences and risk assessment techniques. As a result of these problems the agency has referred problems on six of the color additives to an expert panel of Public Health Service scientists (these are red no. 3, 8, 9, 19, and 37 and orange no. 17). In addition, the FDA has decided to call for new testing of two additional color additives because such additional testing appears to be necessary before a determination of safety can be determined. For this reason the FDA, in the Federal Register[13] is requesting comments on why additional time should not be allowed to resolve these questions. For this reason the FDA has proposed to postpone the closing dates for the use of nine previously listed color additives beyond September 3, 1985. The controversy has been described in considerable detail in a recent publication.[14]

This background explores the nature of what the FDA is doing now with a number of the colors and indicates clearly that the agency is concerned and is acting responsibly. There are additional questions about the color additive FD&C (Food, Drug, & Cosmetic) yellow no. 6 which remains on the provisional list. The studies conducted so far on this compound indicates that it is not carcinogenic to Charles River CD-1 mice. A chronic study in rats was performed and those data are just now being reviewed. In addition, chronic testing of both D&C red no. 33 and D&C no. 36 has been requested by the agency; current data indicate that these do not produce a carcinogenic effect in animals.[15]

The above paragraphs outline the current situation with regard to colors and efforts being made to resolve them. Table 4 lists the colors under study, the due time of the final report. Chronic feeding studies are in progress and results of these must be submitted and evaluated as to compliance with the requirements of the law.

Sweeteners

There is an extensive body of literature on the sugars and sugar alcohols.[12] Sucrose as a natural sweetener has received a great deal of attention from the lay public because of alleged effects on some segments of the population (dental caries, diabetes, obesity, heart disease, hyperkinesis). However, a comprehensive review and evaluation of the literature was made 10 years ago by the Federation of American Studies for Experimental Biology (FASEB) and sugar (sucrose) was essentially given a clean bill of health.[16] There has been no significant change in this acceptance of safety in the consumption of sucrose by the general public. The committee that reviewed sucrose examined all data available on absorption and metabolism, acute and chronic studies, special studies including carcinogenicity, teratogenicity and atherosclerosis, diabetes and dental caries. An overall conclusion, paraphrased, is as follows: "other than the contribution made to dental caries there is no clear evidence that sucrose is a hazard to the public when used at the levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether an increase in sugar consumption would result in a health hazard if there were a significant increase in the total consumption of sucrose, corn sugar, corn syrup and invert sugar."

In addition, the committee specifically discounted the alleged connection between sucrose and the incidence of tumors in laboratory animals.[17] A summary of what the FASEB review proposed is that after careful examination sucrose, like any other natural or added constituent of foods, is not totally without food safety concerns but that the popular association of sucrose with serious chronic diseases is not warranted by the information now available. That view, to our knowledge, is still held by the scientific community in 1986. Thus aside from the real or potential problems associated with tempting foods, particularly candies and pastries, which can and do lead to obesity, there is no known serious primary problem associated with consumption of sucrose.

It is noted here that a separate evaluation was made by FASEB for corn sugar (dextrose), corn syrup, and invert sugar as food ingredients.[18] The high fructose corn syrup is a combination of fructose and dextrose (glucose). Two most useful commercial formulations are 55% and 90% high-fructose corn syrup, the latter 50% sweeter than sucrose. They are used in beverages, salad dressings, pickle products, catsup, baked goods, table-top syrups, fruits, and desserts. High-fructose corn syrup is easy to blend, to store and to ship and there is currently no known adverse effects other than those attributed to any of the caloric sweeteners, namely high caloric intake with high consumption and the danger of obesity. The sugar alcohols are currently (1986) under review by FASEB.

TABLE 5. Urinary Bladder Neoplasia in Rats From the IRDC: Two-Generation Bioassy on Sodium Saccharin

Treatment	No. of rats	Percentage of rats with			
		Transitional cell papilloma	Squamous cell carcinoma	Transitional cell carcinoma	Any neoplasia
Sodium saccharin					
0.0	343	1.2	0.0	0.6	1.7
1.0	684	1.3	0.0	0.7	2.0
3.0	494	1.0	0.0	1.2	2.2
4.0	198	2.0	0.0	5.0	7.1
5.0	125	2.4	0.8	10.4	13.6
6.25	125	4.8	0.8	12.0	16.8
7.50	123	9.8	0.0	22.0	30.9
5.0 through gestation	125	2.4	0.0	0.8	3.2
5.0 after gestation	125	2.4	0.0	0.8	11.2
Sodium hippurate					
3.0	122	0.0	0.0	0.8	0.8

From Squire.[22]

IRDC: International Research and Development Corporation.

Saccharin

Saccharin was discovered in 1879 and has been in commercial use for more than 80 years. It has been investigated, reviewed, and debated more than any other food additive in the United States. A full review and an excellent update of the current status of saccharin comprises the entirety of a special issue of one of the prominent toxicology journals.[19] This issue updates all of the significant information available on saccharin and the reader is referred to that source for further specific information.

Of all of the nonnutritive sweeteners, saccharin is the most prominent one. However, because of the large literature available on this sweetener, only a brief resume will be provided here of the current status.

In a description of saccharin it should be noted that it has been used commercially for more than 80 years to sweeten food and beverages. It is 300 times sweeter than sucrose and is excreted, unchanged in the urine. It has a wide range of application for foods and beverages particularly when it is combined with aspartame or cyclamate; they enhance each other so that the combinations are sweeter than the individual sweetners. Furthermore, saccharin has a stable shelf-life. There are some organoleptic objections to the use of it however by some individuals, the most prominent one being that of a slight metallic aftertaste. For the most part it is used in soft drinks, tabletop sweeteners, and a wide range of other beverages and foods, and also is useful in the cosmetic and pharmaceutical industries.

At least 20 human studies have been completed with no overall association between saccharin intake and bladder cancer, the major concern with respect to neoplasia. The data include a study of 9000 individuals conducted by the National Cancer Institute which concluded that there was no evidence of increased risk with the long-term use of artificial sweeteners in any form including exposure that began decades ago. The most recent study conducted by Jensen *et al.* of the Danish Center Registry[20] concluded that the results of their investigation are in line with the overall absence of bladder cancer risk associated with artificial sweetener consumption in the United States, England, and Japan. These investigators stated that it would be highly unlikely that the consumption of artificial sweetners has contributed to current bladder cancer rates in man.

There have been 14 single-generation animal feeding studies in which the animals were fed saccharin for a lifetime. None of these have shown it to be a cancer-causing substance over a span of one generation. Several studies have found bladder tumors in male rats exposed to high doses of saccharin *in utero* and postnatal periods and in two-generation studies. However, the doses provided were extremely high. A panel of scientists that reviewed a recent study by the International Research and Development Corporation (IRDC)[19] concluded "that the results of the IRDC study, by better defining the dose response relationship for bladder tumor risk in the rat, support the conclusion that the present level of exposure of humans to saccharin through its use as a food additive is unlikely to present a risk for cancer." This study used 2500 rats and several dose levels over extended periods of time.

Tumor incidence in the IRDC study is shown in Table 5, taken from Squire 1985.[21] From the review by Squire, indicating marked injury to the urinary bladder, most likely due to passage of the unchanged saccharin through the urinary system, it was possible to conclude the following: there were compound related increases in the incidences of hyperplasia and/or neoplasia at the 4.0%, 5.0%, 6.25%, and 7.5% dietary levels of sodium saccharin. There was also a small increase in transitional cell carcinomas and in combined papillomas, and carcinomas in the 3% group, however, these differences in the 3% group did not achieve statistical significance. No compound related ef-

fects in either the grade or incidence of any lesions were evident in the 1% group indicating a no effect level.

The conclusions of the expert panel reviewing all data available from studies conducted to date and, in particular, the IRDC study were that the latter study, be defining more sharply the dose–response relationship for bladder tumor risk in the rat, supports the view that the present level of exposure of humans to saccharin through its use as a food additive presents an insignificant cancer risk. The US Senate has voted to allow the continued use of saccharin[22] in human foods and beverages.

Cyclamate

Cyclamate has been removed from the market and therefore will be given only a short consideration in this report. It was banned in the United States in 1970 but currently there is a petition to the FDA to reapprove it. Cyclamate is a noncaloric sweetener, discovered in 1937. It has been used widely in low calorie foods and beverages but, in contrast to saccharin, is only 30 times sweeter than sucrose. This chemical is variably metabolized in the gastrointestinal tract. It is not metabolized by the liver and is excreted by the kidneys unchanged, much the way that sodium saccharin is excreted.

In 1984 the FDA's Cancer Assessment Committee reviewed the scientific evidence and reached the conclusion that "the collective weight of the many experiments indicates that cyclamate is not carcinogenic." In 1985 the National Academy of Sciences[23] reaffirmed this conclusion noting "the totality of the evidence from studies in animals does not indicate that cyclamate or its major metabolite, cyclohexylamine, is carcinogenic by itself." However, before cyclamate can be approved for use in the United States once more the FDA must conduct an extensive review of the National Academy of Sciences report and resolve other questions which relate primarily to the acceptable daily intake for this nonnutritive sweetner.

Cyclamate is approved and used in more than 40 countries worldwide and the Joint Expert Committee on Food Additives of the World Health Organization raised the acceptable daily intake of 4 mg/kg in effect in 1980, to 10 mg/kg body weight an almost three-fold increase in 1982.[12] Additional background history and earlier data relative to cyclamate is available in other publications including an National Academy of Sciences (NAS) publication entitled, *Sweeteners: Issues and Uncertainties.*[24]

Aspartame

Aspartame is the first commercially available noncarbohydrate nutritive sweetener which was approved for table use and other uses in dry mixes by the FDA in 1974.[25] There was an objection to the approval on safety grounds and questions about the authenticity of the test data led to a stay of that approval. After many years of controversy in the literature which will not be covered here, in 1981 the FDA approved aspartame in the United States with a note on the label cautioning "contains phenylalanine" for the benefit of persons with phenylketonuria (PKU), an inborn error of metabolism. Furthermore, there were instructions not to use it in cooking or baking. However, in France, in 1979, and elsewhere in Europe, in 1980, aspartame was approved and received an acceptable daily intake of 40 mg/kg body weight from the Joint Expert Committee on Food Additives, World Health Organization (JECFA) in 1980. With this background data the FDA commisioner noted that "few compounds have withstood such detailed testing and repeated close scrutiny in the process through which aspartame has gone; this should provide the public with additional confidence of its safety."

In 1984 the FDA reaffirmed its conclusion that aspartame can be safely consumed. After a 4-month review of 517 consumer complaints related to the use of aspartame in 1984 the Centers for Disease Control (CDC) found that the complaints "do not provide evidence of the existence of serious, widespread adverse health consequences attendant to the use of aspartame." The CDC further noted that "the majority of frequently reported symptoms were mild and are symptoms that are common in the general population."

The Food and Drug Administration and most all reasonable scientists familiar with the data have concluded that aspartame and its use in a wide variety of products is a safe and useful option for those individuals who prefer low-calorie sweetener. More than 100 scientific tests have provided strong evidence that consuming aspartame is no more hazardous than eating protein in the diet because it is a simple peptide composed of two amino acids, L-phenylalanine and L-aspartic acid. The calories are so minimal that aspartame is considered virtually noncaloric.

Despite the overwhelming evidence of safety for aspartame many objections by a relatively small number of scientists and consumer groups have been raised before and after the sweetener's 1983 approval for use in carbonated beverages. However, the FDA noted that these objections have been dealth with fully in earlier proceedings leading to the approval of aspartame for dry uses.[26] The safety questions primarily concern the potential harmful effects of aspartame's breakdown components. Among other alleged problems was the report by an Arizona researcher that aspartame and soft drinks stored in high heat could break down into its component parts, including methanol[27] and constitute a hazard from that source.

The acceptable daily intake (ADI) for aspartame (50 mg/kg body weight) set by the FDA and reevaluated and

reaffirmed several times is based on a broad array of data including clinical studies in which humans received, with no ill effect, up to 200 mg/kg aspartame per day equal to a human consuming 60 12-oz cans of aspartame sweetened soft drink at one sitting.[28] It has been estimated that if aspartame replaced all the sugar and saccharin in the diet, the highest likely chronic consumption per day would be 34 mg/kg, well below the ADI but also far below any level even suspected of being toxic.

Much of the scientific data on the physiology and biochemistry of aspartame is provided by a recent volume that does an excellent job of covering the scientific data on this interesting sweetener.[28]

Figure 1 shows the chemical structure of aspartame with dotted lines dividing it into its component parts aspartate and phenylalanine, along with methanol. Figure 1 illustrates that the compound can be broken down into its component parts by biological systems, and, as Stegink[28] has pointed out "salt, water, sugar, and even a mother's love produce deleterious effects when given in inappropriate amounts." Figure 2 illustrates the peak plasma level of phenylalanine in normal subjects and in PKU heterozygotes indicating a potential for risk for this subset of the population. This problem has been addressed in FDA cautionary labeling of aspartame. The critical question is whether the compound is potentially harmful at normal use and at potentially abuse levels.

Olney[29] and Reif-Lehrer[30] have shown that aspartame is absorbed and metabolized in one of two ways. It may be hydrolyzed in the intestinal lumen to aspartate, phenylalanine, and methanol by proteolytic and hydrolytic enzymes after which these compounds are absorbed from the lumen and reach the blood the same as other amino acids. Alternatively, aspartame may be absorbed directly into mucosal cells by peptide transport mechamisms with subsequent hydrolysis within the cell to aspartate, phenylalanine, and methanol. In any case, doses absorbed release aspartate, phenylalanine, and methanol to the portal blood and these components must be metabolized and/or excreted.

Whereas the ADI for aspartame has been set at 50 mg/kg, Table 6 shows that a summary of projections for aspartame intake assures that the maximum intake is well below this figure.[31-34] From Table 6 one can see that if aspartame totally replaces the estimated mean daily sucrose intake on a sweetness basis the intake of aspartame will range between 3 and 11 mg/kg body weight. This amounts to 1.7 to 6.2 mg/kg body weight of phenylalanine, 1.3 to 4.9 mg/kg aspartate, and 0.33 to 1.22 mg/kg body weight methanol. The highest daily aspartame ingestion according to these calculations would range from 22 to 34 mg/kg body weight. In comparing the quantity of amino acids contributed by aspartame ingestion at these levels with normal intakes for aspartate and phenylalanine

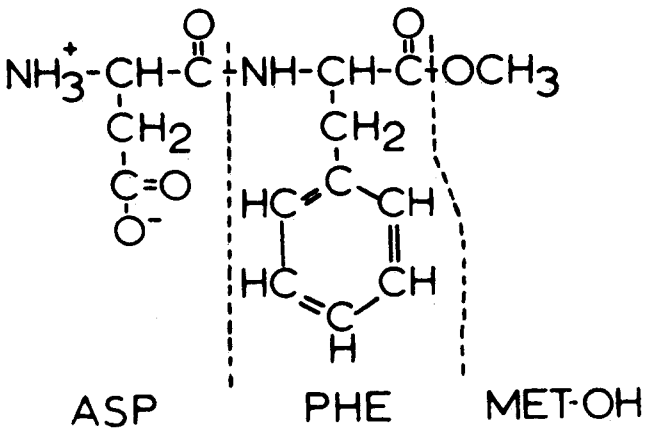

FIG. 1. Chemical structure of aspartame.

provided by dietary protein, yields values ranging from 52 to 229 mg/kg body weight for phenylalanine and from 80 to 395 mg/kg body weight for aspartate per day. Thus, the projected intake levels for aspartame suggest that it will have a relatively small effect on aspartate and phenylalanine intake compared to the normal intake of these amino acids from protein sources in the diet on a daily basis. The work of Stegink and others has shown clearly that even abusive levels of aspartate results in relatively small increases in the phenylalanine content of the plasma or of the red cells. This includes 50 mg/kg body weight of aspartame given to normal lactating females.

The obvious concern is for those members of society who are sensitive to some component of the chemical, principally phenylalanine. Phenylketonuria occurs in one person in every 50 to 75 individuals as a heterozygous state. A number of studies have shown that the phenylketonuria heterozygotes metabolize the phenylalanine portion of aspartame slower than normal subjects. However peak phenylalanine values in these subjects were well below those associated with toxic effects.

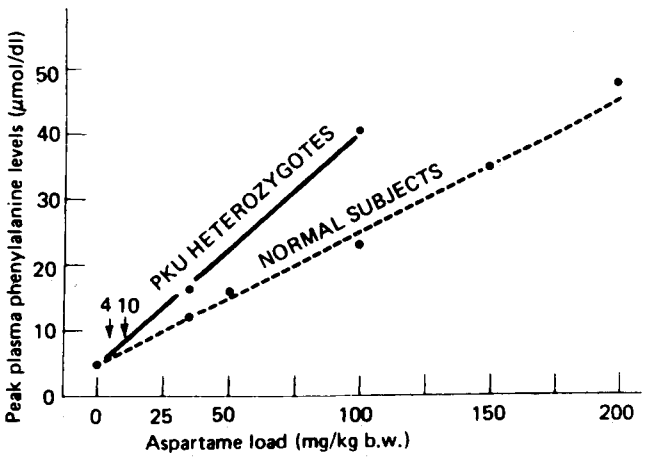

FIG. 2. Mean peak plasma phenylalanine concentrations after exposure to aspartame.

TABLE 6. Projections for Aspartame Intake

Reference	Aspartame totally replacing sucrose	Maximum intake (mg/kg/BW)
FDA	Not calculated	
MRCA	3–11	22–28
Steginк	7–9	25–34
		23–25

FDA: Food and Drug Administration, MRCA: Market Research Corporation; BW: body weight.

With respect to the component methanol, Figure 3 illustrates that the mean blood methanol concentration in normal adults administered aspartame up to 200 mg/kg of body weight. Blood methanol concentrations returned to preloading values 8 hours after administration of 100 mg/kg but were still detectable 8 hours after subjects received 150 or 200 mg/kg body weight.

Many of the toxic effects of methanol in the nonhuman primate are due to formate accumulation, rather than to formaldehyde or methanol, and blood and urine samples from subjects administered the highest aspartame dose caused no reason for concern. These determinations show that there were no significant changes in blood formate concentration after administration of aspartame at 200 mg/kg body weight. Urinary formate excretion was significantly increased over the preloading values at 4 and 8 hours after aspartame loading, indicating minor risk from aspartame's methanol content at the doses studied.

The conclusion from all of the data available on aspartame is that this sweetener is safe for use, particularly under the conditions that it is prescribed, with notations to those people who may be sensitive to it because of special health problems.

Other Sweeteners

Acesulfane K: This is a noncaloric sweetener discovered in Germany; it is under development by the American Hoechst Corporation. It is an intensely sweet organic salt 200 times sweeter than sucrose and, as with the other nonnutritive sweeteners, acesulfane is not metabolized by the body; it is excreted by the kidneys unchanged. The potential uses are similar to those sweeteners currently in use such as hot and cold beverages, dry beverage mixes, baked goods, milk products, veterinary feeds, food preparations, candy and chewing gums, table-top sweeteners, toothpaste, mouthwash, and pharmaceuticals. A large number of safety studies have been conducted and no ill effects reported. Petitions for the use in foods have been filed in several countries including the United States and it recently was approved for use in the United Kingdom, West Germany, and Switzerland.

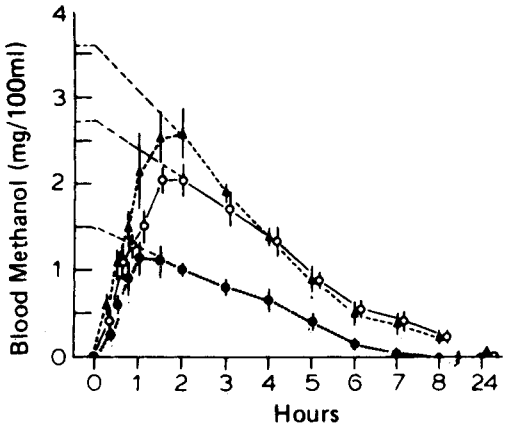

FIG. 3. Mean blood methanol concentrations in normal adults given aspartame up to 200 mg/kg body weight.

Thaumatin (Talin): This product is a mixture of sweet tasting proteins from a west African fruit than can now be grown in a number of tropical and subtropical countries. It is 2000 to 3000 times sweeter than sucrose but the taste develops slowly and it leaves a licorice like aftertaste. It acts synergistically with acesulfane K, saccharin, and stevioside (described below). Thus, it may be useful as a flavor extender for cosmetics and pharmaceuticals with potential applications to beverages and perhaps chewing gums. It cannot be used in products that are to be baked or boiled. Currently thaumatin has been approved in Japan and, recently in the United Kingdom, it has been approved for use in foods and beverages.

Glycyrrhizin: This is a noncaloric extract of licorice roots, 100 times sweeter than sucrose and used as a flavoring agent for tobacco, selected confectionary products, and in some pharmaceuticals. It is also used as a foaming agent in some nonalcoholic beverages. The licorice flavor however limits the potential for widespread use. It is approved in the United States as a flavor and flavor enhancer.

Stevioside: This is an extract from the leaves of a South American plant, 300 times sweeter than sucrose and with a long-lasting sweet taste. It is stable and water soluble. It can be used in soft drinks, chewing gum, fish, sauces, syrups, pharmaceuticals, and table-top sweeteners. Currently it is approved for use in Japan, Paraguay, and Brazil.

Chloroid derivatives of sucrose: These compounds are produced by altering the sucrose molecule. Several derivatives are produced in the process. The sweetness ranges from 5 to 2000 times that of sucrose and the various analogues are potentially useful in beverages, dietetic foods and in orally administered pharmaceuticals. The long-term toxicity research and production technology remain to be accomplished and none of them are currently approved for use anywhere.

Dihydrochalcones (DHCS): These are noncaloric sweeteners derived from bioflavenols of citrus fruits. They range in sweetness from 300 to 2000 times that of sucrose

and there is a delayed sweet taste with a licorice aftertaste. Currently neo-DHC, synthesized from seville oranges, has the greatest potential for food applications. It is about 1500 times sweeter than sucrose and is potentially useful in chewing gum, candies, toothpaste, mouthwash, some fruit juices, and pharmaceuticals. Currently it is approved for use in Belgium, Rhodesia, and Spain.

L-sugars: These are left-handed counterparts of common sugars reportedly not metabolized by humans, noncaloric, no aftertaste and not subject to spoilage. None of them have been approved for use anywhere and extensive testing and improved manufacturing methods will be required before they can be economically feasible.

Caloric Sweeteners

In addition to sucrose and dextrose, there are several caloric sweeteners appropriate for use in different types of dietary products. These are pure crystallized fructose, high-fructose corn syrup, and the polyalcohols, sorbitol, mannitol, and xylotol.

Pure crystalline fructose: This is the sweetest and most soluble of the common sugars and occurs in fruits and vegetables. It is 1.2 to 1.8 times sweeter than sucrose and has a synergistic sweetening effect with other sweeteners. It is used in baked goods, beverages, frozen foods, and in table-top sweeteners. Limitations include a high moisture retention and costly production.

High-fructose corn syrup: The combination of fructose and dextrose (glucose) the 2 most useful commercial formulations are 55% and 90% high-fructose corn syrup (HFCS). They are used in beverages, salad dressings, catsup, baked goods, pickled products, table-top syrups, fruits, and desserts. These products are easy to blend, store, and ship.

Sorbitol: This most widely used sugar alcohol, or polyalcohol, is approximately 0.5 to 0.7 times as sweet as sucrose and is used in special dietary foods including candies and gums. More than 50 to 80 g a day may have a laxative effect.

Mannitol: This polyalcohol is about 0.7 times as sweet as sucrose and is used as a bulking agent in powdered foods and as a dusting agent for chewing gum. Excessive consumption (more than 20 g a day) can have a laxative effect.

Xylitol: This is a polyalcohol derived from fruits and vegetables such as lettuce, carrots and strawberries and also is found in cellulose biproducts of wood, straw, and seed hulls. Xylitol has about the same sweetness as sucrose and is used in chewing gums and in various foods.

With the foregoing data as background it seems reasonable to assume that virtually all of the nonnutritive and nutritive sweeteners now approved are safe under intended conditions of use. Whereas one can envision a certain number of people in a population of more than 200 million to be sensitive to some of them, in general, there appears to be an extremely low rate of sensitivity and this is of only negligible concern, given the cautions that are exercised with the intended use of the products.

Preservatives

Only a few of the more important preservatives will be described here, primarily those which are widely used, some from natural sources.

Butylated Hydroxyanisole and Butylated Hydroxytolulene

These food preservatives (antioxidants) have frequently been criticized but both are GRAS substances limited only by a total antioxidant content of not more than 0.2% of the fat or oil content of foods. They also have regulated food additive uses in dry cereals, shortenings, potato shreds, granules and flakes, ranging from 10 to 200 ppm. They are permitted in dry yeasts and dry beverage and dessert mixes and in beverages and desserts made from dry mixes.

Butylated hydroxytolulene was initially approved by the FDA in 1954 and listed as GRAS in 1959. It prevents degradative oxidation of fats that can lead to undesirable flavor and to the destruction of fat soluble vitamins and essential fatty acids. In addition, without the use of such antioxidants the oxidation that may occur also produces toxic byproducts in the foods. There is roughly 2 million pounds of BHT produced annually for food uses. The BHT has been subjected to GRAS review and to FDA evaluation, but furthermore, it has also been tested in the National Cancer Institute carcinogenesis bioassay program. In both rats and mice, BHT fed at 3000 and 6000 ppm did not reveal any suggestion that BHT was carcinogenic.[35] Since that time however much more work has been done on BHA and BHT. For example, BHT given before carcinogen exposure inhibits mammary tumorigenesis by DMBA and liver tumors induced by dimethylaminoazobenzene.[36,37] There are many other aspects of BHT investigations which can be found in the report by Fukiyama and Hsieh 1985.[38] Butylated hydroxytolulene is thought to inhibit carcinogenesis by stimulating detoxification pathways leading to the excretion of more polar metabolites and to decreased binding of the carcinogens to DNA. The evidence from most studies conducted to date clearly indicates that BHT pretreatment does indeed protect the animal from the carcinogenic effects of a number of chemical carcinogens, primarily by enhancing the detoxification and excretion of the carcinogens.

The phenolic antioxidants including not only BHA, BHT, but also propylgallate (PG), and tertiary butylhydroxic phenol (TBHQ) which are widely used in various

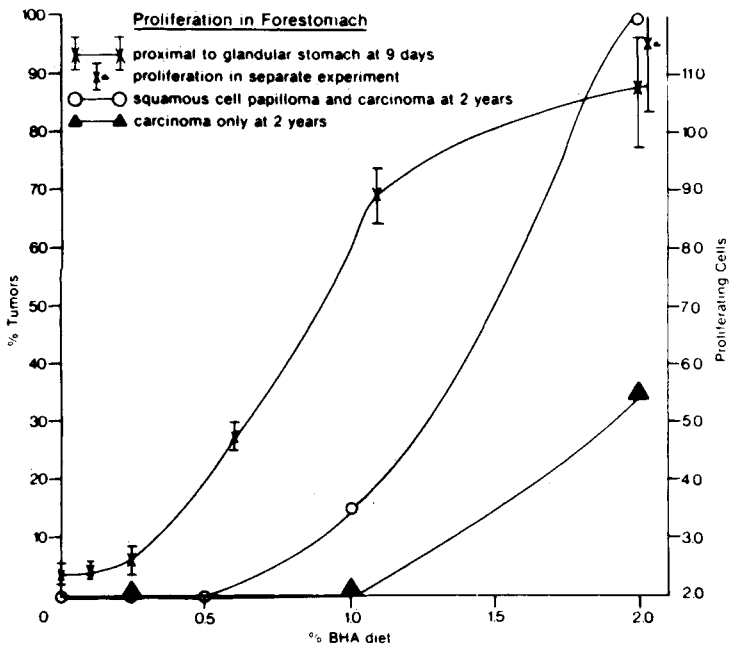

FIG. 4. Dose–response curves of effect of BHA on rat forestomach, comparing short-term with long-term effects.

parts of the world. Until recently BHA was considered to be a very desirable antioxidant from the toxicological point of view. Recent studies however have suggested that BHA can lead to the induction of squamous cell carcinomas and papillomas of the rat forestomach.[39,40]

Recent work from Canada has indicated that both BHA and BHT fed at relatively high levels (up to 2% of the diet) caused proliferative lesions of the squamous epithelium of the forestomach of the rat. These lesions correspond well with those chronic lesions described by Ito *et al.*[40] and indicate that in the rat these two antioxidants do indeed produce proliferative lesions. Figure 4, from Nera *et al.*,[41] shows the composite of lesions observed in short-term studies equated quite well to those observed in the 2-year studies. Although these observations are of concern it should be noted that the lesions have only been observed in the rodent and there is some indication (unpublished) that these changes associated with BHA and BHT are species specific, and then only at high-dose exposure. However, closer scrutiny of these two very important antioxidants will be continued.

Nitrites

Examples of additional important direct food additives include nitrate and nitrite salts. The Food and Drug Administration Food Additive Regulations for these compounds cover their uses in fish products, such as cod roe, and in smoked and cured sable fish, salmon, tuna fish, shad and chub. They are also covered in preparations for the home curing of meats and meat products. A much larger volume of uses for these compounds in meat and poultry products are directly regulated by the US Department of Agriculture (USDA). The latter uses were for many years considered to be prior sanctioned but in 1978 the USDA, although affirming the prior sanction of uses in meat products, denied the prior sanction of uses in poultry products. Also, in 1978 a concern about nitrates and nitrites arose from their demonstrated role in nitrosamine formation and, furthermore, the possibility of direct induction of cancer based on a study conducted at Massachusetts Institute of Technology (MIT) for the FDA. The details of this study and of the use of nitrites and nitrates are covered in great detail in another more recent publication.[42]

The use of nitrates and nitrites may impose some risk on human populations but quantifying the risk has not been satisfactorily accomplished to date. Despite the potential for the production of nitrosamines in food products, nitrites and nitrates are very useful in the prevention of botulism caused by *Clostridium botulinum* spores in meat products. Furthermore, nitrates are widely present in drinking water and vegetables; nitrites themselves are produced endogenously in the human body at levels as high as 70 times more than the amount ingested in meats. Currently nitrates and nitrites are under continuing scrutiny by the regulatory agencies and are being investigated in depth in basic biological studies by the scientific community. Currently, however their benefits appear to outweigh the potential risk.

Contaminants

This report does not deal with foodborne hazards of microbial origin, despite their extreme importance and significance to public health. These considerations are detailed in a number of publications and this review only considers those contaminants that are of natural or man-made origin and about which some exposure information

TABLE 7. Partial List of Major Contaminants of Industrial Origin

Chemical	Source	Foods contaminated
Polychlorinated biphenyls (PCBs)	Electrical industry	Fish, human milk
Dioxins	Impurities in chlorophenols	Fish, cow's milk, beef fat
Pentachlorophenol (PCP)	Wood preservative	Various foods
Dibenzofurans	Impurities in PCP and PCB	Fish
Hexachlorobenzene	Fungidice	Animal fat, dosing products, human milk
Lead	Auto exhaust Coal combustion Canning industry	Grain Vegetables Canned milk
Cadmium	Sewer sludge Smelters	Grains, vegetables, meat products
Arsenic	Smelters	Milk, vegtables, fruit
Tin	Canning industry	Canned foods

Adapted from Munro and Charbonneau.[43]

is known. Table 7 lists major contaminants of industrial origin.

In a survey of the 50 states and 10 federal agencies, the Office of Technology Assessment at the request of Congress identified 243 incidences involving food contamination in the 10-year period between 1968 and 1978. Every region of the United States and every food category were involved. Major incidences included polychlorinated biphenyls (PCB) contamination of the Hudson River, polybrominated biphenyl contamination of animal feed in Michigan and kepone contamination of the James River in Virginia. Other incidences also were reported involving dieldrin, mercury, pentachlorophenol, pentachloronitrobenzene, picloran, chlordane, DDT, toxaphene, parathion, diazenone, and collectively pesticides. A damaged transformer led to PCB contamination of animal fats at a packaging plant in Montana and ultimately hundreds of thousands of pounds of foods in 17 states were affected.[43] The dioxin contamination of the Times Beach incident in Missouri stands as an excellent example of industrial contamination.

Table 8 lists the important natural origin contaminants. Contaminants from natural sources will be subdivided into categories listed in general under intrinsic components of foods of plant origin, metabolites of microorganisms that grow on foods and compounds of natural origin contaminating edible animal products.

Although this is a long list of contaminants of natural origin only a few of them are of significant public health concern. Most all of these contaminants have been adequately dealt with by control mechanisms promulgated by regulatory agencies. The important ones include the aflatoxins, trichothecenes, pyrrolizidine alkaloids, marine toxins, nitrosamines, oxidized fats and polynuclear aromatic hydrocarbons. Since definitive data with respect to these various chemicals are available in numerous references[43–46] to chemicals to which humans are exposed they will not be further alluded to in this report.

The paragraphs and illustrative material noted above suggest that the diet of populations in the United States varies in calories but is relatively high in nutrient density. There are also problems with contaminants, natural and man-made. However the use of food additives are generally justified and are generally safe under the conditions that they are used. Our diet is under continuing criticism by many would-be experts and others who wish to take issue with different aspects of our food supply. Is the US diet safe? It seems clear that the diets consumed by more subsets of our population are indeed safe. Moreover, the diet of North Americans has never been more nutritious.

TABLE 8. Food Hazards of Natural Origin

Intrinsic components of foods of plant origin
Oxylates
Glycoalkaloids of white potato
Cyanogenetic glycosides
Quercetin and related plant phenalics
Hemagglutinins
Phytoalexins
Mushroom poisonings
Goitrogens
Metabolites of microorganisms that grow on foods
Aflatoxins
Patulin
Zearalenone
Trichothecenes
Ochratoxin
Sterigmatocystin
Compounds of natural origin contaminating edible animal products
Coniine
Pyrrolizidine alkaloids
Marine toxins
Compounds produced during food storage processing preparation
Nitrosamines
Oxidized fat
Polynuclear aromatic hydrocarbons and mutagens in cooked food

Adapted from Munro and Charbonneau,[43] Searle,[44] and NAS[45].

We have eliminated the malnutrition of diseases of the past such as pellagra, scurvy, *etc.*, and now must contend more with excesses which are associated with chronic diseases such as arthritis, diabetes, cancer, and others. Despite this, the general health of the American people has never been better. These statements have been supported by many public health officials, in particular, by the US Surgeon General but also by other public health authorities.

The annual death rate has been cut by 50% in this century. Infectious and communicable diseases no longer have the life-threatening potential that they did years ago. Life expectancy increased from 47 years in 1900 to about 74 years in 1985, and continues to improve on an annual basis. Although progress against infectious diseases and the near eradication of nutrition deficiency diseases have contributed to long lifespans, these same increased lifespans have resulted in a larger group of older Americans who inevitably develop some form of chronic degenerative diseases including heart disease, stroke, and cancer as noted above. These are the consequences of a longer lifespan. Indeed, although it is difficult to deal with these complex degenerative diseases, considerable progress is being made.

With respect to environmental and dietary problems, we have never been better off and the prospect for the future looks even more promising. As noted in a number of publications,[45] however, our lifestyle may require closer scrutiny and we may benefit from some modification, particularly with respect to ingested fat. There is reason to be encouraged rather than fearful of food additives which, with cautious use, offer promise of even better health through prevention, rather than therapy.

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