Food Additives and Food Safety

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A brief overview is presented of the number, function, and quantity of food additives used in processed foods. Findings of a recent review of all available information on the safety of over 400 generally recognized as safe (GRAS) food additives are discussed. Hazards of food additives vis-à-vis naturally occurring constituents in foods, natural and accidental food contaminants, and substances that may be formed inadvertently in foods are examined. Despite extensive, but admittedly incomplete, scientific study of the effects of food additives, they are frequently assailed in the media as major contributors to human disease. The available data indicate that such assertions are less than objective for they ignore the possible contributions of natural toxicants in foods, food preparation practices, excessive caloric intake, and dietary imbalances. Procedures proposed for assessing food safety that may improve public confidence and acceptability of food safety issues are discussed.

The past decade has witnessed much public concern about the safety of food additives, particularly those added to processed foods by the food industry. Much of this concern has been addressed to substances which the public identifies as chemicals, e.g., antioxidants and preservatives, as contrasted to substances of natural origin, e.g., herbs
and spices, or, indeed, the myriad chemicals unrecognized by the consumer that are natural constituents of all foods.

The widespread media coverage of the debates on the carcinogenicity of diethylstilbestrol, saccharin, and nitrite has intensified public interest in chemicals being added to foods and has contributed to the public belief that food additives may be a major cause of cancer. As scientists, what can we say in answer to this public perception of the hazards of food additives? What are these substances, what functions do they serve, and what amounts are being added to foods? How do the risks of food additives compare with those of toxicants that occur naturally in foods, and risks of other dietary components? Do the benefits of food additives merit consideration in determining the acceptability of a food additive, and, if so, to what extent? Can the last question be answered solely by scientists involved in this field? If they cannot answer it, who should, and how should it be answered? Can the process of safety assessment be improved to enhance public confidence in the safety of the food supply?

In this paper, I shall try to answer some of these questions. My discussion will be divided into four areas. First, I shall review briefly the classifications, approximate numbers, and amounts of food additives that are used in the food industry; second, I shall discuss the measures taken by the government to ensure the safety of food additives and ongoing work in this area; third, the risks of food additives will be placed in the perspective of the risks associated with toxicants occurring naturally in foods, including natural contaminants, food preparation procedures, and dietary imbalances; and fourth, food policy issues will be addressed, particularly risk/benefit analysis and processes for assessing food safety that may improve public confidence and acceptability of food safety decisions.

As defined by law, there are four principal categories of substances that are intentionally added to foods: (1) food additives, (2) generally recognized as safe food ingredients, (3) prior-sanctioned food ingredients, and (4) color additives (17). Thus from the regulatory viewpoint, the term "food additive" does not encompass all substances which the consumer might consider to be additives.

As defined in the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act (17), "The term 'food additive', means 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 (including any substance intended for use in producing, preparing, treating, packaging, transporting, or holding food...)."

Until the passage of the 1958 Amendment, the responsibility of proving an additive safe lay with the FDA; a food additive was considered safe for its intended use until proved otherwise. The amendment now requires that food additives receive approval from the Food and Drug Administration before they may be added to foods. Approval must be based on scientific data provided by the petitioner which demonstrate the absence of hazard when the substance is used in the amount and manner proposed.

An exception to such prior approval of safety was granted by the 1958 Amendment to substances which are "generally recognized among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use;..." These "generally recognized as safe" substances are commonly referred to as GRAS food ingredients.

The GRAS concept provided a modified grandfather clause to accomplish the evaluation of several hundred food ingredients in use prior to 1958, without requiring extensive additional testing. Another important distinction between food additives and GRAS food ingredients as defined in the 1958 Amendment lies in the application of the Delaney Clause of the Amendment which applies to the former group but not to the latter. The clause states, in part: "...that no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal..." However, other sections of the Food, Drug, and Cosmetic Act give FDA the authority to ban, or restrict the use of, a GRAS food ingredient to safe levels if evidence indicates it may be injurious to health (16).

Prior-sanction means an explicit approval granted prior to 1958 by the FDA or by the U.S. Department of Agriculture for the use of a substance in food [21 CFR 170.3 (51)]. Additives in this category that are listed in the Code of Federal Regulations [21 CFR 181] are substances that were approved for use in the manufacture of food-packaging material. Other unpublished prior-sanctions have been granted.

Rules concerning color additives were prescribed in the 1960 Color Additives Amendment to the Federal Food, Drug, and Cosmetic Act (9). This amendment made the food industry responsible for proving the safety of colors added to foods.

**GRAS Food Ingredients**

The 1980 revision of the Code of Federal Regulations lists about 500 substances currently considered to be GRAS by FDA (51). About 100 additional substances, not listed in the Code of Federal Regulations, were authorized in letters issued by FDA and are regarded by FDA as "unpublished GRAS substances" (49). The original listings of GRAS substances were published in the Federal Register on Nov 20, 1959, and Aug 12, 1960. Prior to publication of these lists, FDA sought the opinions of many qualified individuals for the purpose of eliminating any substance considered to have possible hazard. Several substances were eliminated before initial publication and others have been deleted since. Among the latter are the artificial sweeteners, saccharin and cyclamates, which have been much discussed in the public press in the past two or three years.

The 1958 Amendment did not specify that FDA be the sole judge of GRAS status of a substance; it only required that such recognition of safety be among experts "qualified by training and experience to judge its safety." Almost immediately after the enactment of the Amendment, the Flavor and Extract Manufacturers' Association (FEMA) formed a panel of experts to evaluate the natural and synthetic substances used as flavoring agents in processed foods. Results of these evaluations which identified some 1650 flavoring agents as GRAS were reported in a series of 12 articles published from 1960 (29) to 1979 (52). Of this group, about 730 are included in the Code of Federal Regulations as food additives under the heading "Synthetic flavoring substances and adjuvants." Additional natural products are included in the Code under the heading "Natural flavoring substances and natural substances used in conjunction with flavors" (51). Adding the FEMA GRAS substances to those listed in the Code of Federal Regulations, and including the unpublished GRAS substances, FDA estimated that about 1500 substances currently are determined to be GRAS.
stances, the total number of substances identified as GRAS is about 2250. Of these, about 1750 are flavoring agents.

**Direct Food Additives**

Excluding flavoring agents and related substances, most of which are also included on the FEMA GRAS list, some 270 substances are listed in the 1980 revision of the Code of Federal Regulations as food additives permitted for the direct addition to food (51). Additionally, about 120 substances are listed as secondary direct food additives. Included in this group are processing aids such as ion-exchange resins, clarifying agents, and chemicals used in the lye-peeling of fruits and vegetables. These additives are largely removed from the food product in the processing operation.

These two groups of about 390 substances are additives that have been approved for use in food since 1958. They were approved on the basis of information submitted by petitioners to FDA which established the safety of the additives in food, showed them to be effective in their intended functional uses, and provided analytical methods to allow monitoring their levels of addition to food.

**Functions and Benefits of Food Additives and GRAS Food Ingredients**

Food additives (including GRAS food ingredients) perform a variety of functions in foods. Forty such functions were identified in the 1977 National Academy of Sciences, National Research Council (NAS/NRC) survey of the food industry on the use of food additives (49).

A sampling of additives according to function includes anticaking agents, antioxidants, colors, curing and pickling agents, emulsifiers, enzymes, flavoring agents, leavening agents, nutrient supplements, pH control agents, propellants, processing aids, stabilizers, thickeners, and texturizers. The principal benefits of the use of food additives are cost reduction, user convenience, nutrition, food quality and attractiveness, prevention of microbial contamination, and increase in the variety of foods available to the consumers.

Several examples of the benefits from the use of additives in processed foods can be cited. Development of modern mass production methods for bread, and the resultant lowered production costs, required emulsifiers and dough conditioners (oxidizing and reducing agents, proteases) that compensate for the variability in flour properties and ensure satisfactory operation of the process and consistent quality of the product (28).

The success of cake mixes in assuring the production of a good cake despite gross mistreatment by the home baker is in large measure due to the additives (emulsifiers and leavening agents) included in the formulation (28).

Addition of small amounts of antioxidants protects margarine, shortening, and cooking and salad oils against rancidification by air oxidation, thereby providing the shelf life needed in today’s production and distribution system (69).

Propionates are used to protect bread against mold growth and extend its usable life after purchase. Acidulants are added to a variety of foods to prevent the growth of microorganisms and germination of spores which lead to the spoilage of foods or cause food poisoning or disease (8).

Enrichment of cereal products with vitamins in the 1940’s was a major factor in the elimination of pellagra from this country. The natural level of iron in foods is insufficient to provide the dietary intake of iron recommended by the Food and Nutrition Board for most population groups. Iron enriched cereals now provide about one-third of iron in the U.S. dietary (62).

Flavor and appearance are important factors in the acceptability of food, thereby affecting food choice and nutritional adequacy (56).

**Consumer Exposure**

An important factor in evaluating the possible hazard of a food ingredient is the quantity that is ingested. Information on the dietary intake of the GRAS food ingredients and food additives in processed foods has been provided by surveys of the food industry conducted by the National Research Council on additive usage in 1970, 1975, and 1976 (45,46,49). The 1970 and 1975 surveys were limited to GRAS food ingredients; the 1976 survey included food additives and some GRAS substances. One measure of consumer exposure is the quantity of additive use per capita. Table I lists the 15 GRAS food ingredients used by the food industry in greatest amount in 1975. Annual per capita usage of these ingredients ranged from 23 to 0.07 lb. Included in this group are substances also commonly used in home preparation: sucrose, corn syrup, salt, sodium bicarbonate, yeast, monosodium glutamate, and hydrolyzed vegetable proteins. Use of the other substances is largely confined to commercially prepared foods. Use of sucrose by the food industry appears to have been underreported the 1975 survey. Including use in beverages, total use in processed foods was 70 lb/capita in 1971 (53) and probably was about the same in 1975. Greatest poundage reported for a direct food additive in 1975 or 1976 was 31 million pounds for a modified starch, distarch phosphate. Few other additives were used in amounts exceeding 1 million pounds annually.

Although flavoring agents comprise the majority of substances intentionally added to foods, they are added in relatively small amounts. Those used in greatest quantity by the food industry, and also in the home, are the natural flavoring substances (Table II). Included are such common household condiments as mustard, pepper, cassis (cinnamon), nutmeg, cloves, and allspice. Daily per capita use of the 14 used in greatest amount ranged from 170 to 3 mg.

The 15 synthetic substances used in greatest amounts in flavorings by the processed food industry in 1976 are listed in Table III. Included are substances (adjuvants) which aid or modify a flavor, or serve as solvents or carriers (adjuvants) for flavors. Isopropyl alcohol and acetone were used as flavoring and as solvents for other

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**Table I. GRAS Food Ingredients Used by Food Industry in Largest Quantities in 1975 (45)**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Annual Use</th>
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<tbody>
<tr>
<td></td>
<td>million lb</td>
</tr>
<tr>
<td>sucrose</td>
<td>5000</td>
</tr>
<tr>
<td>corn syrup</td>
<td>1530</td>
</tr>
<tr>
<td>sodium chloride</td>
<td>1420</td>
</tr>
<tr>
<td>dextrose</td>
<td>266</td>
</tr>
<tr>
<td>mono- and diglycerides</td>
<td>86</td>
</tr>
<tr>
<td>hydrochloric acid</td>
<td>82</td>
</tr>
<tr>
<td>caramel</td>
<td>74</td>
</tr>
<tr>
<td>sodium bicarbonate</td>
<td>60</td>
</tr>
<tr>
<td>yeasts</td>
<td>57</td>
</tr>
<tr>
<td>citric acid</td>
<td>57</td>
</tr>
<tr>
<td>calcium phosphate, monobasic</td>
<td>48</td>
</tr>
<tr>
<td>monosodium glutamate</td>
<td>28</td>
</tr>
<tr>
<td>carbon dioxide</td>
<td>27</td>
</tr>
<tr>
<td>hydrolyzed vegetable proteins</td>
<td>23</td>
</tr>
<tr>
<td>sodium aluminum phosphate</td>
<td>15</td>
</tr>
</tbody>
</table>
flavorings. Synthetics were generally used in lesser quantities in processed food than the natural flavorings. Per capita exposure of the 15 used in greatest quantity ranged from 104 to 0.11 mg/day. None of those listed in Table III is commonly used in the home preparation of foods. Although prepared synthetically, many are natural constituents of foods; for example, of the flavorings listed in Table III, malic acid, ethyl acetate, thiamine, isobutyl acetate, isoamyl butyrate, and butyric acid occur naturally in fruits, cheeses, and other foods.

For all flavorings, natural and synthetic, 78% were used by the food industry in 1970 or 1976 in quantities less than 1000 lb, 61% less than 100 lb, and 38% less than 10 lb.

Evaluation of Safety of Additives

Procedures deemed most applicable to the evaluation of food chemicals at the time of the 1958 Amendment, and which continue to be used as part of present day protocols, were described in terms of studies in rats and dogs of acute oral toxicity, subacute oral toxicity, and chronic (2-year) oral toxicity (47). From the highest dietary level at which no adverse effects were observed in the chronic toxicity tests, a safe level of intake for man was estimated by incorporating a substantial safety factor. This safety factor (48) has been arbitrarily set at 100; i.e., the safe level in food is expressed at $1/100$ of the experimentally determined no-adverse-effect level [21 CFR 170.22].

In addition, the petitioner for approval of a food additive was required to submit information on the purposes, i.e., the intended effect for which the additive was proposed, the amount required to accomplish this purpose, and practicable analytical methods for the additive that could be used for control purposes [21 CFR 171.1].

The exemption from biological testing for GRAS food ingredients in use before 1958 was of some concern. Consequently, the President, upon recommendation of the White House Conference on Food, Nutrition, and Health (79), directed FDA in 1969 to critically evaluate the scientific literature on these substances. Reviews of the scientific literature on individual GRAS substances, or groups of related substances, included approximately 400 substances and were organized in 118 monographs by several commercial institutions under FDA contracts. The National Academy of Sciences, National Research Council surveyed the food industry to determine the levels of use of each GRAS substance in food, the poundage used, and to estimate daily human intakes (49). FDA also awarded a series of contracts for mutagenic and teratogenic testing of selected GRAS substances, as well as conducting teratogenic testing within its own laboratories. The documents resulting from the above contracts were provided to the Federation of American Societies for Experimental Biology (FASEB) for review, evaluation, and conclusions concerning the health aspects of using each of the GRAS substances in food. These evaluations were undertaken in 1972 by the Life Sciences Research Office (LSRO), a division of the Executive Office of FASEB. Supplemental information was collected by LSRO by literature searches and contacts with governmental and private sectors.

The evaluations of the data on the assigned GRAS food ingredients were undertaken by a group of eleven qualified scientists chosen by FASEB as consultants, and designated as the Select Committee on GRAS Substances. Members were selected, for the most part, from nominations made by the constituent societies of FASEB. Their evaluations were made independently of FDA or any other governmental or nongovernmental group.

The judgments of safety by the Select Committee were usually expressed in the form of one of five different conclusions which FDA translated into regulatory action (32).

(1) There is no evidence in the available information on that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future (FDA interpretation: Substance continued in GRAS status with no limitations other than good manufacturing practice.)

(2) There is no evidence in the available information on that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard. (FDA interpretation: Substance continued in GRAS status with limitations on the amounts that can be added to food.)

(3) While no evidence in the available information on demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies should be conducted. (FDA interpretation: Issue an interim food additive regulation requiring commitment, within a stated period, that necessary testing will be undertaken. Substance continued in GRAS status while tests are conducted.)

Table II. Natural Flavoring Substances Reported Used by Food Industry in Largest Amounts in 1970 and 1976, NAS/NRC Surveys (46, 49)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Usage 1000 lb/year</th>
<th>mg/capita day</th>
</tr>
</thead>
<tbody>
<tr>
<td>mustard, yellow</td>
<td>31 000</td>
<td>170</td>
</tr>
<tr>
<td>pepper, black</td>
<td>19 051</td>
<td>108</td>
</tr>
<tr>
<td>malt extract</td>
<td>7 050</td>
<td>40</td>
</tr>
<tr>
<td>pepper, red</td>
<td>2 334</td>
<td>14</td>
</tr>
<tr>
<td>caffeine</td>
<td>2 000</td>
<td>11</td>
</tr>
<tr>
<td>lemon oil</td>
<td>1 547</td>
<td>9</td>
</tr>
<tr>
<td>cassia</td>
<td>1 147</td>
<td>7</td>
</tr>
<tr>
<td>oregano</td>
<td>920</td>
<td>5</td>
</tr>
<tr>
<td>peppermint oil</td>
<td>870</td>
<td>5</td>
</tr>
<tr>
<td>nutmeg</td>
<td>770</td>
<td>4</td>
</tr>
<tr>
<td>caraway seed</td>
<td>634</td>
<td>4</td>
</tr>
<tr>
<td>cocoa extract</td>
<td>536</td>
<td>3</td>
</tr>
<tr>
<td>cloves</td>
<td>519</td>
<td>3</td>
</tr>
<tr>
<td>allspice</td>
<td>498</td>
<td>3</td>
</tr>
</tbody>
</table>

Table III. Synthetic Flavoring Substances, Adjuncts and Adjuvants, Reported Used in the Largest Amounts in the 1977 NRC Survey (46)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Usage 1000 lb/year</th>
<th>mg/capita day</th>
</tr>
</thead>
<tbody>
<tr>
<td>monosodium glutamate</td>
<td>18 000</td>
<td>104</td>
</tr>
<tr>
<td>isopropyl alcohol</td>
<td>4 000</td>
<td>17</td>
</tr>
<tr>
<td>malic acid</td>
<td>3 000</td>
<td>17</td>
</tr>
<tr>
<td>acetone</td>
<td>570</td>
<td>3.3</td>
</tr>
<tr>
<td>ethyl acetate</td>
<td>560</td>
<td>3.2</td>
</tr>
<tr>
<td>methyl salicylate</td>
<td>280</td>
<td>1.6</td>
</tr>
<tr>
<td>ethyl acetateacetate</td>
<td>63</td>
<td>0.36</td>
</tr>
<tr>
<td>4-(methylthio)-2-butanone</td>
<td>59</td>
<td>0.34</td>
</tr>
<tr>
<td>thiamine hydrochloride</td>
<td>57</td>
<td>0.33</td>
</tr>
<tr>
<td>isobutyl acetate</td>
<td>44</td>
<td>0.25</td>
</tr>
<tr>
<td>ethyl maltol</td>
<td>28</td>
<td>0.22</td>
</tr>
<tr>
<td>isoamyl butyrate</td>
<td>36</td>
<td>0.21</td>
</tr>
<tr>
<td>butyric acid</td>
<td>27</td>
<td>0.15</td>
</tr>
<tr>
<td>triacetin</td>
<td>20</td>
<td>0.13</td>
</tr>
<tr>
<td>acetaldehyde</td>
<td>19</td>
<td>0.11</td>
</tr>
</tbody>
</table>
are being completed and evaluated.)

(4) The evidence on —— is insufficient to determine that the adverse effects reported are not deleterious to the public health when it is used at levels that are now current and in the manner now practiced. (FDA interpretation: Establish safe usage conditions or rescind its GRAS status. Interested parties may submit a petition establishing conditions of safe use.)

(5) In view of the almost complete lack of biological studies, the Select Committee has insufficient data upon which to evaluate the safety of —— as a food ingredient. (FDA interpretation: Provide interested parties opportunity to submit relevant data for evaluation or rescind its GRAS status.)

In its evaluation of the information on 415 GRAS substances, the Select Committee reached conclusion no. 1 on 75.5%, no. 2 on 15.2%, no. 3 on 4.5%, no. 4 on 1.2%, and no. 5 on 3.6%.

Considerations leading to conclusion no. 2 for 15% of the substances included relatively narrow margins of safety between the intake of high consumers from processed foods and the no-adverse-effect level in animals (sulfiting agents), or between the intake from processed foods and dietary supplements and the amount that causes toxic manifestations in humans (vitamins D and A); evidence that a proportion of the population may be sensitive responders to the substance (dextran, monosodium glutamate); or insufficient data to ensure that interaction with food constituents would not result in hazardous products if higher concentrations or more rigorous treatments were employed (hydrogen peroxide as a bleaching agent).

Conclusion no. 3 was reached for butylated hydroxyanisole and butylated hydroxytoluene based upon liver hypertrophy and microsomal enzyme induction observed in animal feeding studies with these antioxidants. It is unknown what relationship and possible significance this enzyme induction may have with respect to the metabolism of widely used drugs and dietary constituents by microsomal hydroxylases.

Nutmeg, mace, and their essential oils were given no. 3 conclusions based on uncertainties of the health effects and content of safrole (a weak carcinogen) and myristicin (a reported hallucinogen) in the products.

Conclusion no. 3 was accorded caffeine as an ingredient in cola beverages because of uncertainties concerning its effects as a central nervous system stimulant. The Select Committee concluded that undesirable behavioral effects might be induced in children from the consumption of caffeine from infancy through adolescence, even though these potential effects are neither adequately documented nor are their consequences clear.

After consideration of the available evidence on sucrose, the Select Committee concluded that, other than its contribution to dental caries, there is no clear evidence that demonstrates sucrose is hazardous to the public health when used at the levels that are now current and in the manner now practiced. It was not possible to determine without additional data whether an increase in sugar consumption, that would result if there were a significant increase in the total of sucrose, corn sugar, corn syrup, and invert sugar added to foods, would constitute a dietary hazard. Overconsumption of sucrose probably contributes to obesity and possibly results in dietary imbalances and modifications of lipid metabolism which potentiate coronary heart disease. Also, sucrose is among the most cariogenic of all the carbohydrates tested but dental caries can and does occur in people who have never used sucrose or processed foods. It was the Select Committee’s opinion that informing the consumer of the sugar content of foods by appropriate labeling would allow a more judicious selection of sweetened foods, and that choices could be made easier with a greater selection of less sugared foods in the marketplace.

The basis for the no. 4 conclusion for sodium chloride was its role as a contributing factor to essential hypertension in the 10–30% of the U.S. population that is genetically predisposed to this condition. The Select Committee opined that a lowered daily consumption of sodium chloride promises health benefits for the proportion of the population susceptible to hypertension. Adequate labeling of the sodium content of foods was proposed as a useful measure in helping to reduce sodium consumption. Recognizing that sodium and chloride are essential nutrients and that the balance among sodium, potassium, and chloride in the diet is of great importance, particularly to individuals with certain disease conditions, the Committee recommended that guidelines be developed for lowering the salt content of processed foods. Such guidelines should preclude nutrient imbalances such as the recent occurrence of hypochloremia in infants consuming an infant formula low in chloride content (59).

The possibility of trace residues of a derivateizing reagent (epichlorohydrin) found to have carcinogenic properties was the basis for the no. 4 conclusion on certain modified starches. However, the industry had discontinued use of this reagent as soon as its carcinogenic properties were discovered.

Natural Toxicants in Food

No hazard to public health has been revealed in the Select Committee’s analysis of the available information on 95% (conclusions 1, 2, and 3) of the 415 GRAS food ingredients evaluated to date when used in processed foods at current levels and in the manner now practiced. However, uncertainties in the data on 4.5% (conclusion 3) of these required that additional studies should be conducted to answer specific questions. Among the substances on which questions were raised, or limitations suggested on their use, were nutrients and other natural components of food, e.g., vitamins A and D, glucose, sucrose, glutamic acid, and caffeine. Additional perspective on the relative hazards of intentional food additives (including the GRAS food ingredients) may be gained by further consideration of the biological properties of some natural food constituents.

Rutabaga, turnips, cabbage, cauliflower, and other vegetables of the genus *Brassica* contain glucosinolates that hydrolyze to goitrins, e.g., substances that promote thyroid enlargement or goiter (73). It has been suggested that consumption of these cruciferous plants could be a factor contributing to endemic goiter in some parts of the world where iodine content of the diet is low. Indeed, goiter has been attributed to the consumption of large amounts of cabbage or of kale that have been shown to be high in thiocyanate, isothiocyanate, and goitrin. Glucosinate composition of varieties of both common and Chinese cabbages has been determined to provide a data base for the evaluation of newly developed cultivars in regard to their content of these toxicants.

Potatoes contain the toxic glycoalkaloid solanine (78). The safety margin for solanine is approximately 10. In humans, an oral dose of 200 mg causes drowsiness, hypotension, and dyspnea, while higher doses result in vomiting and diarrhea. The normal range of solanine in potatoes is 2–13 mg/100 g fresh weight; however, in certain isolated cases concentrations as high as 80–100 mg/100 g fresh weight have been reported, as in the “greening” in
smaller tubers exposed to light. An experimental variety, Lenape, under development a few years ago for the potato chip industry had excellent physical properties but was found to have an unusually high glycoalkaloid content. Development was discontinued and since that time alkaloid analyses have become a part of new variety development.

Cyanogenetic glycosides that release hydrogen cyanide upon hydrolysis occur in several food plants. Montgomery (43) reports that lima beans, cassava, sweet potato, chickpea, sorghum, and bamboo are food plants capable of producing HCN. Cases of cyanide poisoning by lima beans have been documented. The cyanide content of lima beans varies according to variety. A white-seeded American variety produced 10 mg HCN/100 g of seed, whereas a white Burma variety yielded 200 mg and a black Puerto Rican variety produced 300 mg/100 g of seed. The lethal dose for the adult human is reported to be in the range of 50–250 mg. Chronic neurological disease in certain tropical countries has been attributed to the cyanide intoxication from dietary cassava.

Protein inhibitors of proteolytic enzymes, particularly against the pancreatic proteolytic enzymes of vertebrates, have been found in soybeans, lima beans, peas, and potatoes (35).

A mushroom, the false morel, *Gyromitra esculenta*, contains a hydrazine, N-methyl-N-formyl hydrazine, that has been reported to be a potent carcinogen in mice (74). The common domestic mushroom, *Agaricus bisporus*, also contains a hydrazine derivative, agaritine, which is being tested for carcinogenicity (63).

There are a number of naturally occurring vasoactive amines that greatly increase blood pressure when they enter the peripheral circulation of man or animals (38). Among the compounds is tyramine that occurs in cheese and/or tyramine and serotonin that are found in bananas, red plums, avocados, and tomatoes (76). They are rapidly inactivated in vivo by monoamine oxidase and seldom cause problems when taken orally. However, for patients under monoamine oxidase inhibitor therapy, ingestion of such foods could be potentially dangerous.

The flavonoids, kaempferol and quercetin, which occur as glycosides in many fruits, vegetables, and tea (31,41), have been demonstrated to have mutagenic activity in the Ames test toward *Salmonella typhimurium* strains TA-98 and TA-100 (4,39). Pamukcu et al. (54) recently reported that rats fed diets containing 0.1% quercetin developed intestinal and bladder cancers. However, Ambrose et al. (1) reported no carcinogenic effects in rats fed diets containing 1% quercetin. These discrepant findings may be resolved by animal feeding tests with quercetin that FDA has requested the National Toxicology Center to conduct (30).

The concern of FDA regarding natural toxicants in food crops is expressed in section 170.30 (Title 21) of the Code of Federal Regulations. This section states that any food crop widely consumed for its nutrient properties prior to Jan 1, 1958, will have its GRAS status reviewed if its composition has been significantly altered by breeding or selection after that date, and if the change may be reasonably expected to alter the concentration of toxic constituents. However, I am not aware of any systematic programs of FDA in this area.

The foregoing compounds are examples of natural food components that have been identified as toxicants, usually as a result of adverse effects experienced by man from ingestion of large amounts of a particular food. Other examples of toxic plant constituents could be cited, but the toxic properties of the majority of plant constituents have yet to be studied. Thus, foods present a complex mixture of chemicals, whose safety has been determined largely by experience. In contrast, food additives are compounds of known structure whose toxic properties have been studied, levels of addition controlled, and which have wider margins of safety.

Another class of toxicants that may be present in certain foods is the mycotoxins, natural contaminants that result from mold growth on agricultural crops in the field or post-harvest in storage. Best known of these is aflatoxin, a product of the fungus, *Aspergillus flavus*, that is widespread in its occurrence (26). Aflatoxin is a potent carcinogen in rats and has been found in peanuts, corn, cottonseed, tree nuts, and a number of other commodities. Depending on the levels fed, aflatoxin and/or a metabolite, also carcinogenic, may be detected in the tissues of farm animals, particularly the liver, or the milk in the case of dairy animals. The Delaney Clause does not apply to naturally occurring contaminants. FDA has set an action level of 20 ppb aflatoxin in food and feed products, and 0.5 ppb in fluid milk (22) under the provisions of 21 CFR 109, recognizing that aflatoxin cannot be avoided by good manufacturing practice, but that technology changes may enable a further reduction of action levels.

Although epidemiological studies in five countries in southeast Asia and Africa showed a positive correlation between the level of intake of aflatoxin and incidence rate of primary liver cancer (77), no difference was found in incidence of this disease in the U.S. between regions of expected high and low exposures (68).

Other mycotoxins found to occur in food and feeds are zearalenone, ochratoxin A, trichothecenes, patulin, and penicillic acid (58).

**Other Health Aspects of Natural Dietary Compounds**

As mentioned earlier, the widespread media coverage of the debates on the carcinogenicity of diethylstilbestrol, saccharin, and nitrite has intensified public interest in chemicals being added to foods and has contributed to the public belief that food additives may be a major cause of cancer. However, food additives are the most tested components of our diet and, in the opinion of many, are unlikely to contribute significantly to the incidence of cancer. Gori (27) estimated that 60% of cancers in women and 40% of those in men are related to diet and nutrition. Ames (2) stated that much of the cancer occurring today appears likely to be due to the ingestion of natural carcinogens in the diet. According to Handler (30), there is no known epidemiological evidence that food additives are hazardous to health. Man-made chemicals are a “trivial aspect of the burden of disease,” and the issue is “very emotional.” He said the 80–90% of cancers attributed to environmental causes does not refer to man-made chemicals. In a statement summarizing papers presented and discussions taking place during the Sixth Annual Marabou Symposium held in Stockholm, Sweden, June 1978, on the relationship between food and cancer, it was stated “Of the potential sources of harm in foods the largest by far are, first, microbiological contamination and next, nutritional imbalance. Risks from environmental contamination are about 1000 times less and risk from pesticide residues and food additives a further 100 times smaller again. Naturally occurring compounds in food are far more likely to cause toxicity than intentional food additives” (75).

Cancer incidence data collected by the National Cancer Institute in seven metropolitan areas in 1937–39, 1947–48, and 1957–60 revealed significant increases in cancer of the stomach, colon, and liver in men and cancer of the stomach in women. This increase was greatest in the midwest and southwest regions of the United States. During the same time period a significant decrease in the incidence of cancer of the lung in women was noted. The increase in cancer of the stomach and liver appears to be associated with the consumption of foods that are high in salt. The decrease in cancer of the lung in women appears to be due to a decrease in smoking. The increase in cancer of the colon appears to be due to the consumption of foods that are high in calories and fat. The decrease in cancer of the breast in women appears to be due to a decrease in the consumption of calories and fat.
and 1969–71 indicate little change in the overall incidence of cancer, except for lung cancer, in the last 20-year period (12). Lung cancer now occurs among more people than cancer of any other anatomic site. Epidemiological studies indicate that the major risk factor for lung cancer is cigarette smoking (25). Epidemiological evidence for an association between dietary fat and colon cancer has been presented by Wynder and associates (57,81,82). They noted that a world-wide correlation exists between colon cancer and fat consumption in various countries; its incidence is higher in first and second generations of Japanese migrants in Hawaii and California compared with Japanese in Japan, consistent with their adopting the higher-fat Western diet. They also reported that rats fed a higher-fat diet are more susceptible to colon tumor induction by known carcinogens than rats on a low-fat diet. They hypothesized that bile acids and cholesterol modified by intestinal bacteria are carcinogenic, cocarcinogenic, or tumor promoters in the colon.

In a recent review of colon cancer epidemiology, MacLennan (40) points out that there is a high correlation between colon cancer and protein (meat) consumption as well as total fat consumption. A high correlation was found between colon cancer mortality and intestinal concentration of dihydroxycholanic acid, a bacterial metabolite of bile acids. However, recent studies of colon cancer incidence in Scandinavia suggest that colon cancer has multifactorial etiology (33,72). The results suggested that dietary fiber may have a protective role toward the development of colon cancer. Lipkin (37) points out that factors associated with colon cancer include meat consumption, low dietary fiber content, economic status, geographic exposure, economic development, and genotypic predisposition.

A positive correlation also exists between dietary fat and mortality from breast cancer in several countries of the world (7). Age-adjusted mortality from breast cancer in humans shows a 5- to 10-fold difference between countries with a per capita intake of 50 g/day or less and countries with an intake of 140 to 150 g/day (7). A number of studies have shown that high-fat diets increase the incidence of mammary and skin tumors in mice and rats (5,15,64,71). High-fat diets also tend to be high in calories and this may be a factor in susceptibility to carcinogenesis (3,13). It has been proposed that the level of nutrition and/or dietary fat probably predisposes to breast cancer by changing the hormonal balance (3,13,75). However, it is noted that nonnutritional factors, such as age at birth of the first child and heredity, are also important.

**Food Preparation and Food Safety**

Foodborne diseases resulting from contamination with bacterial pathogens such as various species of Salmonella, or enterotoxins elaborated by staphyloccocal organisms, have long been recognized (6). Food mishandling resulting in disease outbreaks now occurs largely in food service establishments and homes as compared to food processing establishments.

More recently, it has been found that reaction of food constituents during food processing or in home-cooking can result in the formation of potentially toxic products. A similar example is the production of carcinogenic polycyclic aromatic hydrocarbons in the charcoal broiling of meats (36). Formation of these compounds has been attributed to the pyrolysis of fat falling on the heated coals; the pyrolytic products are then absorbed by the meat. Another example is the formation of the toxic amino acid, lysinoalanine, during the heating of protein particularly under alkaline conditions. This was found to occur during the commercial isolation of proteins from alkaline solutions (11,61), and also has been demonstrated to occur in home-cooking of frankfurters, chicken, and egg white (67). However, in view of the small quantities formed in the home-cooked foods or commercial proteins, and the relatively low toxicity as indicated by animal feeding studies, there appears to be little health hazard from this source.

Recently Sugimura and associates (44,70) have found that mutagenic substances are formed in the charred surface of broiled beef and fish which could not be accounted for by aromatic hydrocarbons. Based on the mutagenic activity toward *Salmonella typhimurium* TA-98 in the Ames system, the dimethyl sulfoxide extract of 5.2 g of charred substance from the surface of beefsteak was equivalent to 855 µg of benzo(a)pyrene. Tars obtained by pyrolysis of several amino acids were also mutagenic in the Ames test. The mutagenic compounds formed by the pyrolysis of tryptophan and glutamic acid have been isolated and identified. Mutagenic activities of these compounds toward *S. typhimurium* TA-98 were greater than that of aflatoxin B₁, but were considerably less than the activity of aflatoxin B₁ when tested against *S. typhi-
murium* TA-100.

Mutagenic activity toward *S. typhimurium* TA-1538 has been reported in autoclaved beefstock and cooked ground beef (14). Little or no mutagenic activity was formed in ground lean beef cooked at 100 °C for 10 min in a microwave oven or an electric broiler, but did result when the meat was cooked at surface temperatures in the range of 190–210 °C in a frying pan or electric hamburger cooker. The investigators stated the mutagens formed were neither benzo(a)pyrene nor the mutagens reported in the charred surface of broiled meat and fish. Similar findings were reported by Parzia et al. (55) and Spingarn and Weisburger (66). In view of the relationship shown between mutagenic activity and carcinogenic activity (42), this aspect of food preparation deserves further study.

**Food Safety Policy**

The preceding discussion reflects the opinion of many that the natural components of foods, food selection including excessive caloric intake, and food preparation methods probably present far more hazards to health than do food additives. Nevertheless, it would be generally agree that this is not a justification for placing an untested food additive in the food supply, or for not reviewing the safety of existing additives in light of current concepts of toxicological testing and interpretation. In regard to the latter point, FDA plans to review the some 1650 flavoring substances that are generally recognized as safe. They also plan to conduct periodic reviews of the safety of food additives, both direct and indirect (18).

The concern about the safety of food additives, pesticides, and other chemicals that may enter the food supply has raised questions regarding the testing protocols that would provide the best estimate of risk of adverse effect at the expected level of consumer exposure. Several corollary issues have been raised. For example, should all food substances, GRAS food substances as well as food additives, and natural components of foods as well as substances intentionally added, be subjected to the same protocols to demonstrate their safety? Should risk/benefit assessment be the basis for safety evaluation of food ingredients, or should decisions be based on risk alone? Can an acceptable risk of cancer be defined, i.e., should the Delaney Clause be modified? And who shall participate in the safety assessment?

The Select Committee on Flavor Evaluation Criteria (60) and the Food Safety Council (23) have proposed com-
prehensile systems for measuring risk in a stepwise fashion, either rejecting a substance as unsafe or proceeding through additional tests and then accepting or rejecting the substance. The Food Safety Council has recommended that risks associated with all products that enter the food supply should be assessed according to the same criteria whether the product is a natural food component or a substance intentionally added to food, or whether it is currently classified as a GRAS food ingredient or a food additive (24). The Council noted, however, that practical considerations will affect the way this consistency principle can be put into effect. The American Chemical Society has expressed the view that there should be a uniform regulatory policy applicable to all components of foods: foodstuffs, food additives, and food components (19). The Select Committee on Flavor Evaluation Criteria agreed with this principle insofar as it applies to GRAS flavoring substances. The Select Committee on GRAS Substances recommended that a single unified system of regulation should be applied to all commercially added food ingredients and the GRAS category be eliminated by the year 1990 (65). Thus, there is wide agreement that common criteria should be used in judging the safety of food components, at least for those that are intentionally added.

The Food Safety Council advocates the use of risk: benefit assessment as a valuable aid in making food safety decisions. The only requirement of the present law in this respect is that a proposed additive achieve its intended effect as, for example, preserving, stabilizing, or flavoring. The law does not otherwise require or prohibit assessment of health, economic, or other benefits of the proposed additives with the exception mandated by the Delaney Clause that no food additive shall be deemed to be safe if it is a carcinogen for man or animals. The Food Safety Council points out that FDA has considered benefits as well as risks in setting tolerances for natural contaminants in food (24). For example, in proposing to lower the permitted level for aflatoxin in peanuts and peanut products to 15 ppb, FDA took into account the need to preserve a "highly nutritious and useful food" (21). In 1978, Dr. Donald Kennedy, then Commissioner of FDA, stated that FDA approves a drug because it has a favorable risk:benefit ratio for a particular condition, although provisions of the law do not set out clearly the obligation to balance health risks against health benefits (34). He observed that "if a drug appeared to have a powerful ameliorating action on a life-threatening disease, every sensible drug reviewer tolerated more 'give' in the safety data." Unfortunately, the rules for "give" and "take" are not written down or uniformly followed.

Consideration of benefits in making safety decisions on food additives was included in the recommendations of the NAS Committee for a Study on Saccharin and Food Safety Policy (50). This Committee was formed pursuant to the Saccharin Study and Labeling Act of 1977 (PL 95-203) which requested that the National Academy of Sciences examine the risks and benefits to health of the use of saccharin and consider the more general issues surrounding Federal food safety policy. It recommended that FDA should be responsible for obtaining assessment of benefits, in cases where they can be estimated or objectively assessed, so as to assist the judgment of the agency. However, it considered that risk should be the central factor in food safety regulation. The Committee concluded that in a few unusual cases, FDA may find that high-risk foods or substances may have offsetting benefits of such importance that FDA should be authorized to permit their marketing through restricted channels, or with appropriate labelling, for limited purposes, to limited categories of the population.

Both the American Chemical Society and the American Medical Association have recommended that relevant benefits and risks be taken into account in regulatory actions on food safety and that statutory alternatives to a total ban be available (19).

The NAS Committee observed that benefits, including physiologic, psychologic, and economic aspects, may be difficult to estimate and almost never can be expressed in commensurate units (50). In this regard, the Food Safety Council proposes a two-step process in risk:benefit assessment (24). First, net risk would be estimated by comparing health risks with health benefits; e.g., risks to lives would be compared with lives saved. (The use of nitrite as a curing agent in meat would be an example of a food substance having health benefits and potential health risks.) If this calculation shows a net risk, then this net risk would be compared with benefits, which could include nutritional benefits, supply, cost, convenience, and appeal benefits. To aid decision-making, the Council proposes that benchmarks be set that define the boundaries of acceptable risk and acceptable benefits. Only substances whose risks are below and whose benefits are above these benchmarks would be considered for introduction into the food supply.

This proposal poses the problem of specifying an acceptable level of risk. Traditionally, a safety factor of 100 has been applied to the "no-adverse-effect" level derived from animal feeding studies in which the substance in question has been administered at multiple dosage levels, at least one of which is associated with a toxic response. However, for certain essential nutrients and naturally occurring food constituents, the margin of safety has been described as substantially narrower (10,65). Greater concern is generally expressed for irreversible lesions than for those effects which normalize when the dose is lowered. Examples of irreversible effects include cancer, mutations, and certain birth deformities. Present law (Delaney Clause) states there is no acceptable risk level for a food additive demonstrated to be a carcinogen in animals. The moratorium placed by the Congress on the ban proposed by FDA on saccharin and the request that the National Academy of Sciences examine the benefits as well as the risks to health of the use of saccharin suggest that Congress has interpreted public opinion as approving risk:benefit assessment of food substances found to be carcinogenic in animals, at least for substances that have been in the food supply for a considerable period and for which there are no ready replacements. Whether this is predictive of a modification of the Delaney Clause remains to be seen.

Setting values for maximum acceptable risk and minimum benefit levels is a critical problem in a risk:benefit system of safety assessment. This is particularly true in case of risk of cancer or other irreversible effects. Although the estimation of risk and quantification of benefits, including economic consequence, can be made with some degree of confidence by scientists and economists, the identification of acceptable risk and benefits in any particular case is a societal judgment involving the public at large. One way to meet the problem would be for the Congress, as representatives of the public, to set these levels, or otherwise provide definitive guidelines for the balancing of risk and benefit.

Wodika (80) has suggested that a possible solution to the problem would be to create a large committee selected as a probability sample of the population to decide the borderline cases on the basis of evidence presented by
scientists. He believes there would be general agreement on decisions reached by any mechanism on substances associated with high or low potential risk; only decisions reached on substances of intermediate risk would be highly debatable and would require reference to the committee. According to Wodika, decisions on these substances of intermediate hazard are likely to be unnecessarily stringent if made by regulatory officials who tend to be conservative, whereas consumers without adequate guidance are likely to make undesirably loose decisions.

The Food Safety Council has proposed three alternative decision-making processes and structures in the present regulatory system as it concerns food substances. They range from a minimal change, that would require food safety decision-makers to take into account a risk:benefit assessment before reaching a decision, to a major restructuring of the regulatory system. Their recommended alternative envisages no major change in the role of present regulatory agencies, but would create a committee structure that would complement the existing system. A committee on food safety standards would be established by and be responsible to Congress for the purpose of setting standards of “unacceptable risk” and “minimum benefit.” Having set these standards, the committee would be discharged. A second committee, a food safety assessment committee, chaired by the FDA Commissioner would have responsibility for evaluating and resolving the conflict between food safety and benefits where difficult decisions are involved. Membership on this committee would be nominated by the major groups with a stake in food safety, including organizations representing the consuming public and producers. The committee would produce recommendations for the Commissioner’s approval and would be expected to provide increased confidence in the process of food safety decision-making.

In this brief review, I have discussed the classification and numbers of substances added to foods, the regulations regarding food safety, the possible risks from food additives in the perspective of risks from natural toxicants, and some evolving concepts of assessing food safety. Hopefully, this information will help clarify the role of food additives in food safety.

Many of the substances used in largest amounts by the food industry are also those that have widest discretionary use in home food preparation. Very few are added to processed foods in excess of ounces per capita per year. Despite extensive, but admittedly incomplete, scientific study of the effects of food additives, they are frequently assailed in the media as major contributors to human disease. The available data indicate that such assertions are less than objective for they appear to ignore the possible contributions of natural toxicants in foods, food preparation practices, excessive caloric intake, and dietary imbalances.

In view of the likelihood of continued development of increasingly sensitive methods of chemical analysis for detecting carcinogens in our food supply, and the increasing sophistication of toxicological evaluations identifying now unsuspected adverse health effects, it is evident that new knowledge will demand new approaches to food safety. It is difficult to envision that it would ever be possible to subject each food substance to complete toxicological evaluation. Science, industry, government, and the public must accept the responsibility for carefully and critically building a system of food safety assessment that is logical, efficient, cost-effective, and scientifically objective. Such a system should render socially acceptable decisions, lessen public controversy, and restore and enhance public confidence in the safety of our food supply. How these goals are to be reached is unclear, but we have the opportunity and responsibility to ensure that our food supply continues to be—as it is today—the safest in the world.

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