Carcinogens and Mutagens That May Occur in Foods

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The principal carcinogens and mutagens that have been identified in human foods are reviewed. These agents may occur in foods as naturally occurring components (*e.g.*, metabolites made by plant or fungal cells), components of contaminating plants or microorganisms, food additives (usually unintentional), or products that arise during processing or cooking. In the mixed diets of developed countries the levels of the known carcinogens and mutagens are very low. However, serious contamination of foods by the potent hepatocarcinogen aflatoxin B_1 has occurred in some parts of the world; contamination by N-nitroso compounds or their precursors is another important concern. Extrapolation of the data on the carcinogenicity and mutagenicity of chemicals that can occur in foods to an accurate estimation of the potential hazard to human populations is not yet possible.
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IN THE LAST 20 YEARS the results of epidemiologic studies have provided strong evidence that some factors related to the human diet may have major determining influences on the probability of the development of cancer by the human.[1] Dietary situations that appear to result in increased incidences or mortalities from specific cancers as well as dietary situations that seem to decrease these incidences or mortalities have been identified. Although several mechanisms may be of importance in the modulation of cancer incidences by dietary means, one mechanism through which dietary components have the potential to increase the incidences of cancers is by exposures of individuals to carcinogens that may occur in foods. The occurrence of carcinogens in some foods, either as natural constituents or as inadvertent contaminants that develop during harvesting, processing, or cooking, is now well established and is the subject of this review.

Mutagenesis and Carcinogenesis

The specific linear arrangement of the purine and pyrimidine bases in the cellular DNA (*i.e.*, the cellular genome), through coding for RNAs and subsequently for proteins, determines the potentialities of a cell.[2] Through highly faithful replication of the DNA before each cell division the genome of the parent cell is transmitted essentially unchanged to future cell generations. However, errors in the replication of the DNA may occur at a very low probability, and the probability that an error will occur increases on exposure to ionizing radiations, certain chemicals, or certain viruses. Any alteration in the purine and pyrimidine sequence of the DNA of a daughter strand, as compared to that of a parent strand, constitutes a mutation. If the alteration is compatible with the life and replication of the cell, the mutation usually becomes a permanent part of the DNA and is inherited by all of the progeny of the cell.

In the case of mutagenesis by chemicals, the modifications usually result from reaction of an electrophilic chemical (either the chemical that contacted the cell or a reactive metabolite formed from it) with one of the purine or pyrimidine bases in the DNA to form an adduct. The adduct may cause a mutation directly by preventing accurate replication of the DNA at that site. Alternatively, faulty "repair" of the altered DNA by cellular enzymes may lead to a modification of the DNA that is perpetuated in subsequent cell generations. These mutations may involve only one base pair of the DNA, or they may involve deletions, additions, or rearrangements of polydeoxynucleotide segments. Some mutations have relatively little effect on the structure or function of the cell. In other cases, depending both on the gene involved and the kind and position of the alteration, the mutation may cause a readily observable alteration in cellular structure or function, or both.

The mutations of most concern for this discussion are those that contribute to carcinogenesis (Fig. 1). The great majority of chemical carcinogens, either directly or, more often, as a result of metabolism by the cell, are strong
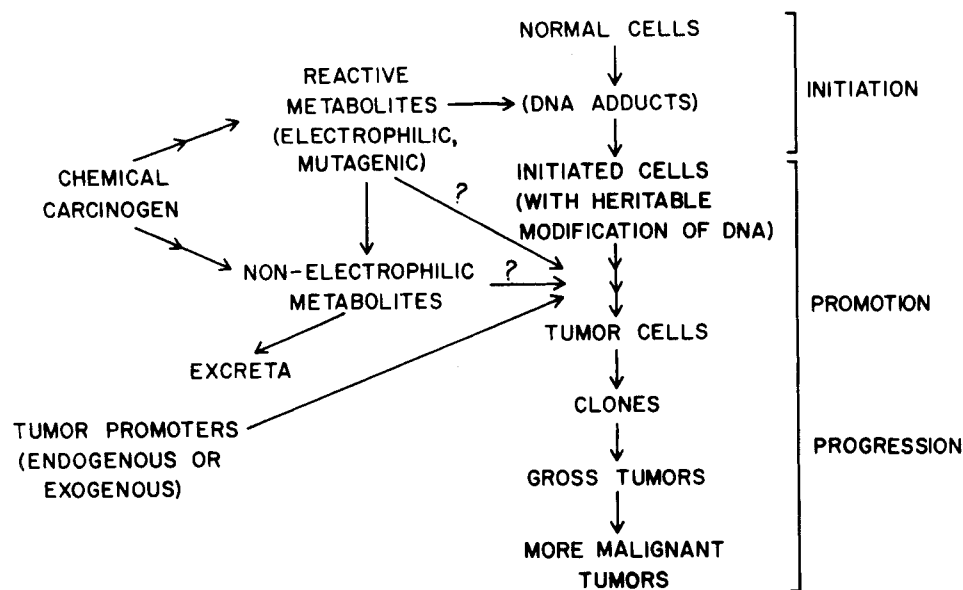
FIG. 1. Diagrammatic representation of the multistage process of carcinogenesis induced by chemical carcinogens alone or with tumor promoters.

electrophilic reactants, and these electrophilic reactants can react with cellular DNA to cause mutations.[3,4] Some mutations cause an apparently irreversible change of a normal cell to one that is predisposed toward becoming a tumor cell (*i.e.,* an "initiated" cell[5]). When exposed at some later time to an appropriate further series of stimuli (by agents collectively called tumor promoters), the initiated cells, through poorly defined steps, give rise to gross tumors.[5] Tumor promotion is generally considered to involve both further modification of the initiated cells and hyperplasia of the initiated cells and their progeny. Whereas tumor initiation occurs rapidly and is largely irreversible, tumor promotion requires repetitive stimuli and appears to be at least partially reversible. Until recently, specific DNA targets for mutagenesis that might be involved in the conversion of normal cells to tumor cells were unknown. However, mutation at specific sites of genes, collectively called proto-oncogenes, is now known to predispose appropriate cells to malignant transformation.[6–8]

Figure 1 also shows other aspects of chemical carcinogenesis. The metabolism of chemical carcinogens generally occurs along several pathways. Although one or more of these pathways cause the conversion of the administered chemical to electrophilic derivatives that can initiate carcinogenesis, other metabolic pathways convert the carcinogen to nonelectrophilic, noncarcinogenic derivatives. Furthermore, the electrophilic metabolites react with other tissue constituents in addition to DNA. As a generalization, increasing the fraction of a carcinogen that is metabolized by activating, as compared to inactivating, pathways and increasing the amounts of metabolites covalently bound to the cellular DNA will enhance the carcinogenic activity. The balance between activating and inactivating metabolism differs between the tissues of a given species and between species and thus accounts for some of the tissue and species specificities of chemical carcinogens.[9] The balance also can be altered under some dietary conditions.[10]

Radioactive Elements in Foods

Any ionizing radiation can give rise to mutations and cancer when the radiation alters the DNA of cells that may later divide. Many of the elements that make up our natural chemical world have radioactive isotopes, *i.e.,* elements that have the same chemical properties as the nonradioactive forms, except that they decompose with the liberation of ionizing radiations. Radioactive isotopes have occurred naturally since the beginning of the universe, and natural phenomena are, by far, the major source of radioactive isotopes. The fraction of an element that occurs as radioactive isotopes, the frequency of decomposition of the radioactive isotopes, and the types of ionizing radiation that are emitted differ as a function of the chemical element. However, any radioactive element or any chemical that contains a radioactive element will be absorbed and utilized by living cells in the same manner as for the corresponding nonradioactive isotope or chemical. The uptake will be in proportion to the fractional contents of the radioactive and nonradioactive isotopes in the soil or groundwater.

As a result practically all foods contain some, but usually very low levels, of a variety of radioactive atoms.[11] The levels of individual radioactive atoms reflect the contents of these atoms in the soil and water in which plants are grown. Likewise, the contents of these atoms in animal

products are a function of the radioactive atoms in the animal's food supply. The most prevalent of the radioactive atoms in foods is potassium 40. Potassium is an essential component of all cells, and the natural occurrence of potassium 40 is 0.01% of all potassium atoms. The potassium 40 in each person, on an average, provides about 25% of the background radiation to the cells of the body. Other radioactive isotopes that are consumed by human populations in water and food include rubidium 87, carbon 14, radium 226, radium 228, and polonium 210. Decomposition of these isotopes in the human body provides, on an average, about 10% as much radiation to body cells as does the decomposition of potassium 40, but because the radium and polonium isotopes are deposited preferentially in bone, they provide 15% to 25% of the radiation that reaches bone marrow cells and other cells adjacent to bone.

Chemical Carcinogens That Are Metabolites of Some Plants Used as Foods

In addition to the proteins, nucleic acids, carbohydrates, and lipids that make up the major structural and functional components of organisms, cells of most organisms synthesize a large number of chemicals of lower molecular weight.[12] These include intermediates in the synthesis of structural components, as well as pigments, cofactors, hormones, and, for at least some species, defenses against predators. The number of different low molecular weight components in common foods is not known, but for many foods it may be in the range of hundreds to thousands. Most of the low molecular weight organic components in plants occur in small amounts, and most have not received toxicologic testing. However, among the small molecular weight metabolites of some plants and fungi used as foods a few chemicals have been shown to be carcinogenic in animals (Fig. 2).

Bracken Fern

Cattle that forage on bracken fern (*Pteridium aquilinum*) as the major component of their diet were observed about 25 years ago to develop hematuria and cancer of the urinary bladder within 2 to 5 years.[13] Administration of dry bracken fern to rats as about one third of their diet for 4 to 6 months or longer resulted in the development of cancers of the urinary bladder, gastrointestinal tract, and mammary gland. Mice and guinea pigs also were susceptible to this carcinogenic activity. Ptaquiloside, a β-glucoside recently isolated from bracken fern, is a relatively potent carcinogen for the induction of mammary cancer on administration to female rats and appears to be a major carcinogenic component of the fern.[14] Other constituents previously have been suggested to contribute to the carcinogenicity of bracken fern, but these data are
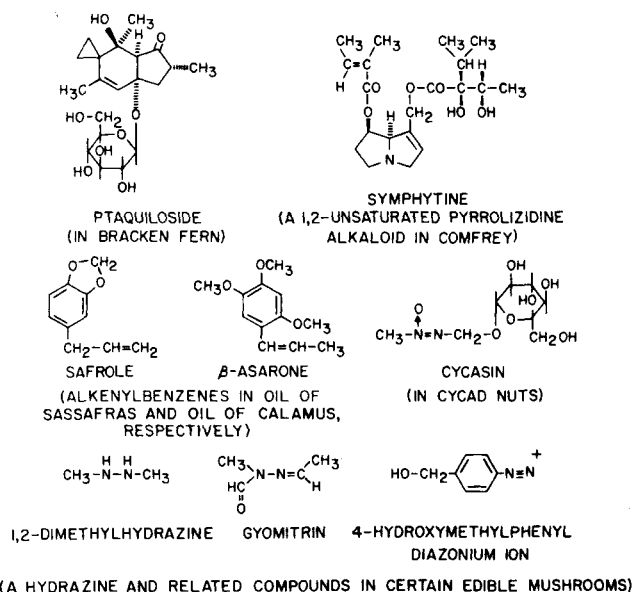

FIG. 2. Examples of carcinogenic chemicals that are metabolites of some green plants and fungi used as foods.

controversial. Thus, long-term consumption of quercetin, a mutagenic component of bracken fern and of a wide variety of other plants, appeared to induce urinary bladders tumors in rats,[15] but this result was not confirmed by other investigators.[14,16] Although bracken fern is used to some extent as a food in Japan and as a salad delicacy in some areas of the United States, the fraction of human diets consumed as bracken fern appears to be very small compared to the levels received by Turkish cattle or the experimental rodents noted above.

Cycasin

The starchy endosperm of the nuts of cycad tree ferns of the family Cycadaceae, after extraction with water to remove toxic materials, has served as a source of food for some native groups in Guam, Kenya, and the Miyako Islands of Japan.[17] Studies carried out about 20 years ago showed that cycad nuts are carcinogenic on oral administration to rats and demonstrated that one of the components, cycasin (methylazoxymethanol β-glucoside) (Fig. 2), is a potent carcinogen for the liver, kidney, and intestine of rats. Cycasin is readily hydrolyzed by bacterial β-glucosidases in the gastrointestinal tract to methylazoxymethanol, which is further metabolized to the potent alkylating agent methyldiazonium hydroxide.[18]

Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids occur in many plant species, including members of the Senecio, Crotalaria, and Heliotropium genera, in amounts from traces up to as much
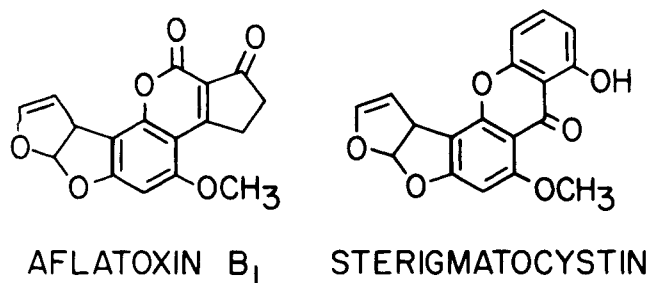
AFLATOXIN B₁   STERIGMATOCYSTIN

FIG. 3. The hepatic carcinogens aflatoxin B₁ and sterigmatocystin, which can occur in foods as a result of contamination by *Aspergillus* species.

as 5% of the dry weight.[19-21] Although many pyrrolizidine alkaloids are relatively nontoxic, some members of this group that contain a 1,2-double bond (Fig. 2) are quite potent toxins for the liver and lungs of rodents and of certain livestock. Large doses of some of these unsaturated pyrrolizidine alkaloids have caused acute toxicity. Low doses of some of them have shown carcinogenic activity on administration to rats[19,20] or mice.[21a] Cytochrome P-450-dependent oxidation of the 1,2-unsaturated pyrrolizidine alkaloids in the endoplasmic reticulum of liver and other tissues converts them to strongly electrophilic pyrrolic esters which are the probable ultimate carcinogens.[19,21] In addition, both the pyrrolic alcohols and/or 4-hydroxy-2-hexenal, both of which may be formed from the pyrrolic esters *in vivo*, may have some role in the toxicity and carcinogenicity of the pyrrolizidine alkaloids.[21-23] Some plants containing the unsaturated pyrrolizidine alkaloids have been used by humans as foods, herbs, drugs, or teas.[19,20,24] Contamination of grain crops, including those used for preparation of flour, by plants containing the pyrrolizidine alkaloids also has occurred and has resulted in serious toxicity to some human populations.[24]

Alkenylbenzene Derivatives

Numerous allylic and propenylic benzene derivatives occur in essential spice oils from a wide variety of plants.[25] Among these naturally occurring compounds safrole (a major component of oil of sassafras), estragole (present in tarragon, sweet basil, and fennel), methyl eugenol (found in sweet bay, cloves, and lemon grass), isosafrole (in ylang-ylang oil), and β-asarone (a major component of oil of calamus) have weak to moderate carcinogenic activity in the livers of mice and/or rats[26,27] (Fig. 2). These agents occur in mixed human dietaries at very low levels.[28] In mouse liver activation of the allylic benzene derivative safrole occurs by hydroxylation at the 1′-position and subsequent conversion of the allylic alcohol to a very reactive sulfuric acid ester, which is the ultimate carcino-

gen.[29] The ultimate carcinogenic metabolites of the propenylic benzene derivatives have not been elucidated.

Hydrazines

At least three common edible mushrooms (the false morel *Gyomitra esculenta*, *Agaricus bisporus*, and *Cortinellus shiitake*) contain hydrazines or hydrazine derivatives (Fig. 2).[18,30,31] Two hydrazines and one hydrazine derivative from *Gyomitra esculenta* (*i.e.*, N-methyl-N-formylhydrazine, N-methylhydrazine, and acetaldehyde methylformylhydrazone), which are present as approximately 0.5%, 0.001%, and 0.03%, respectively, of the wet fungus, have induced significant incidences of tumors in rodents.[30,31] Carcinogenicity assays for agaratine (β-N-[γ-L-(+)glutamyl]-4-hydroxymethylphenylhydrazine), which occurs as up to 0.04% of *Agaricus bisporus* and has also been found in *Cortinellus shiitake*, have not yet been reported. However, the N-acetyl derivative of 4-hydroxymethylphenylhydrazine, a degradation product of agaratine, induced lung and blood vessel tumors in mice.[31] Multiple injections of 4-hydroxymethylphenyldiazonium ion, a degradation product of agaratine which occurs in the mushroom, also induced tumors of the skin and subcutaneous tissue in mice.[32] Since the human consumption of *Agaricus bisporus* in the United States in 1975 was estimated at 160 million kg,[31] further examination of the potential contribution of mushroom consumption to human exposures to carcinogens is needed.

Chemical Carcinogens That Are Metabolites of Microorganisms or Plants That May Contaminate Food Crops

Pyrrolizidine Alkaloids

The pyrrolizidine alkaloids are an important example of carcinogens that can enter the food chain as metabolites of plants that contaminate foods. Thus, in addition to being used intentionally as foods, as discussed above, plants containing toxic 1,2-dehydropyrrolizidine alkaloids can occur as contaminants in grains and other plants used as foods.[24] This contamination has been well documented as a cause of both livestock and human poisoning. Plant species that contain these toxic pyrrolizidine alkaloids occur worldwide, and their total elimination as contaminants of food plants appears to be very difficult.

Aflatoxins

A contaminant of considerable concern with regard to its potential carcinogenic effect in some human populations is aflatoxin B₁, a metabolite of *Aspergillus flavus* and *A. parasiticus* (Fig. 3).[33-36] Aflatoxin B₁, through its metabolism to a very reactive epoxide, is the most potent carcinogen known for the liver of the rat, and it has also

demonstrated carcinogenic activity in a broad range of other species. Both *A. flavus* and *A. parasiticus* are common contaminants of foods that are harvested and/or stored under warm, humid conditions. Epidemiologic data have correlated aflatoxin B_1 contamination of native food with the high levels of hepatic cancer that occur in some populations of Africa and the Far East.[33] However, the interpretation of these data is complicated by correlative data that also implicate hepatitis B virus infection with the development of hepatic cancer in these same areas.[37] A reasonable assessment is that both aflatoxin B_1 and hepatitis B virus infection have etiologic roles under some conditions and that they may be cooperative etiologic agents.[38] Because of the potent carcinogenicity of aflatoxin B_1 and the human epidemiologic data aflatoxin contamination of foods, especially peanuts, corn, and some grains, has been monitored quite closely in the US and most other industrialized countries.[33,35] The levels of contamination appear to have dropped substantially over the last two decades, and the levels reported in the US in recent years generally are very low, even in relation to the high activity of this chemical as a carcinogen.

In addition to aflatoxin B_1, concern has also been expressed for contamination of some foods by related compounds. Aflatoxin M_1, a hepatocarcinogenic metabolite of aflatoxin B_1, occurs at very low levels in the milk of cows that have ingested the parent aflatoxin.[33,35] Both aflatoxin G_1, another metabolite of *A. flavus*, and sterigmatocystin, a related carcinogen formed by *A. versicolor*, are less potent carcinogens than aflatoxin B_1 and apparently are present in contaminated foods at lower levels than aflatoxin B_1, but the data are much less complete than for aflatoxin B_1.[33,35]

Other Mold Toxins

A number of other mold products (*e.g.*, luteoskyrin, ochratoxin A, patulin, T-2 toxin, zearalenone) have been considered as food contaminants that may have roles in the development of cancer in the human.[19,35,36] However, the data on the carcinogenic activities of these products and of their levels in foods are much too limited for a critical consideration of this issue.

Chemical Carcinogens That May Be Formed in the Processing and Cooking of Foods

N-Nitroso Derivatives

N-Nitroso amines, after metabolic activation, and N-nitroso amides are strong alkylating agents, and many of these compounds are potent carcinogens.[39] Nitrite added to food and that formed by bacterial reduction of nitrate reacts under appropriate conditions with amines or amides, which are present in the food as degradation
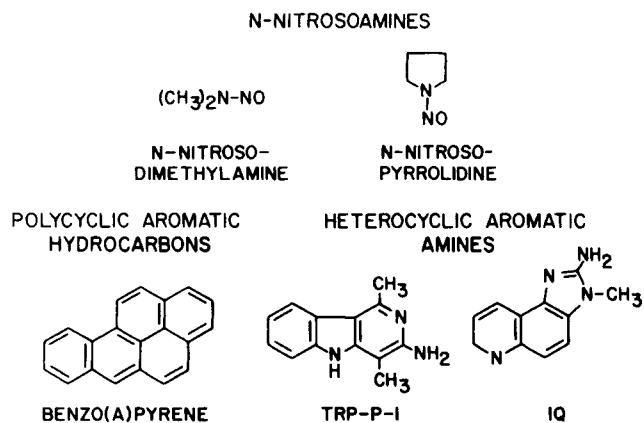

FIG. 4. Examples of carcinogenic chemicals that can occur in foods as a result of reactions that take place during processing or cooking.

products of proteins or other food components, to yield nitrosamines or nitrosamides. N-Nitrosodimethylamine (Fig. 4) is the most frequently found volatile nitrosamine in cheeses, beer, and nitrate–nitrite-preserved meats. Some nitrate–nitrite-preserved meats also contain N-nitrosopyrrolidine and N-nitrosopiperidine, and the content of N-nitrosopyrrolidine frequently increases on cooking. Some N-nitroso amino acids have also been detected in nitrite-preserved meat. Over the last 20 years the levels of nitrate and nitrite added to foods have been markedly lowered and ascorbic acid has been added to inhibit the nitrosation reaction. As a result the contamination of nitrate–nitrite-preserved meats by N-nitroso derivatives has decreased appreciably.[40] Recent studies from several countries indicate average intakes from food of volatile nitrosamines of 0.6 to 2 μg per person per day,[40,41] but the actual values depend on the food habits and food preparation. Until recently contamination of beer with N-nitrosodimethylamine provided the major source of volatile nitrosamine intake in Germany (and presumably other western countries), but modification of the malting procedure to avoid contact of the malt with hot air containing nitrogen oxides has probably largely eliminated this route of contamination.[40] Nonvolatile N-nitroso derivatives in foods have received relatively little study, but N-nitroso-3-hydroxypyrrolidine has been found in nitrite–nitrate-preserved meats at low levels.[40]

Since many N-nitrosoamines and amides are very potent carcinogens for many species of animals,[39] it is prudent to be diligent in eliminating or reducing the levels of human exposure to these compounds. However, the complete elimination of N-nitroso derivatives from foods appears difficult. Nitrate and nitrite occur to some extent in almost all water sources, and these ions are readily taken up by growing plants. Furthermore, the consumption of nitrate and nitrite in food and water, the facile reduction of nitrate to nitrite by bacteria in the mouth,

and the availability of amines and amides from certain medicines, decomposition of foods, and tobacco makes possible the synthesis of N-nitroso derivatives in the mouth and gastrointestinal tract.[42,43] Although the significance of N-nitroso compounds obtained in food or synthesized in the gastrointestinal tract to the incidences of human cancers currently is not clear, the data that are accumulating suggest these compounds may have important roles under some conditions.[43] A dietary situation of particular significance may be the ingestion of high levels of nitrate by individuals simultaneously exposed to nitrosatable amines.[44]

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons, including carcinogens such as benzo(a)pyrene, are formed during incomplete combustion of essentially all carbonaceous material and are released to the environment in the smoke from forest fires or other combustions, including those that give rise to automobile exhaust. Similarly, smoking of meat or fish or cooking foods by processes (*e.g.,* charcoal grilling) in which fat drips onto the heat source and is pyrolyzed can cause contamination of the food by benzo(a)pyrene (Fig. 4) and related hydrocarbons.[45] The levels of these hydrocarbons in the food are generally quite low (approximately 1–10 ng of benzo(a)pyrene per g), and this contamination can be prevented if a barrier is inserted between the source of the hydrocarbon and the meat. Environmental pollution also can contribute to hydrocarbon contamination of foods.[45] Thus, plants grown in badly polluted air have shown low concentrations of benzo(a)pyrene (up to 10 ng/g), presumably from deposition of air pollution particulates on the growing plant. Bivalve molluscs, such as clams and oysters, readily accumulate polycyclic aromatic hydrocarbons from contaminated waters, so most commercial samples of these foods that have been analyzed contain at least trace levels of benzo(a)pyrene (up to 100 ng/g); vertebrate fish, on the other hand, do not appear to accumulate detectable levels of polycyclic aromatic hydrocarbons.

Heterocyclic Aromatic Amines

Several years ago Japanese investigators showed that, in addition to the polycyclic aromatic hydrocarbons, the burned part of charred foods contains heterocyclic aromatic amines, some of which are much more potent mutagens for *Salmonella typhimurium* TA98 and TA100 than is benzo(a)pyrene.[46–48] Detailed analysis of this problem showed that these strongly mutagenic amines are formed by pyrolysis of protein, and that each amino acid gives rise to one or more unique heterocyclic aromatic amines. The products formed by pyrolysis of tryptophan, glutamic acid, and phenylalanine are especially potent

mutagens, whereas the amines formed from some other amino acids have much lower mutagenic activity. Some of these products, *i.e.,* Trp-P-1 (3-amino-1,4-dimethyl-5H-pyrido[4,3]indole), Trp-P-2 (3-amino-1-methyl-5H-pyrido[4,3]indole), Glu-P-1 (2-amino-6-methyldipyrido-[1,2-a:3',2'd]imidazole), and Glu-P-2 (2-aminodipyrido-[1,2-a:3',2'd]imidazole), which are pyrolysis products of tryptophan and glutamic acid, are also carcinogenic on administration in the diets of rodents (Fig. 4).[47] Other highly mutagenic heterocyclic aromatic amines, which are imidazo[4,5-f]quinoxaline derivatives, were first isolated from broiled sardines or fried beef and were later obtained on purification of heated solutions of creatinine, sugar and amino acids. Three of these compounds, designated as IQ, MeIQ, and MeIQx, also are carcinogenic on oral administration to rodents.[47] However, up to the present the activities of these carcinogens are of a lower order of magnitude than was predicted on the basis of their extremely high mutagenicities for the bacterium. In general, the level of the mutagenic activity in meat increases with the time and temperature of cooking and varies with the water content.[48,49] However, the correlation of the formation of some mutagenic products with the Maillard reaction (condensation between a free amino group on an amino acid or protein with the carbonyl group of a sugar moiety) suggests that the complete elimination of all mutagenic heterocyclic amines from cooked food may not be possible.[48]

Food Additives as Potential Sources of Carcinogens

Intentional or unintentional food additives are other potential sources of carcinogens in foods, and nearly all countries have regulations that govern the use of these additives. In the US the levels of food additives are controlled by the Food and Drug Administration, and its actions in relation to possible carcinogenic additives are based primarily on the 1958 Delaney amendment to the Pure Food and Drug Act.[50] This act requires the Food and Drug Administration to ban foods that contain substances that are carcinogenic for animals or humans. This act also accorded GRAS (generally recognized as safe) status to some then commonly used additives for which there were no data indicating significant toxicity. Although this legislation was quite reasonable for the state of knowledge of toxicology and of analytical chemistry 30 years ago, it is less satisfactory today. Thus, knowledge of carcinogenesis and of the activities of carcinogens has provided rational reasons to be more concerned about the intake of some carcinogens than of others. Furthermore, the tremendous strides in analytical methodology now make possible the detection of some contaminants at very low levels that may have very little biological significance.

A wide variety of chemicals are intentionally added to foods, usually in relatively small amounts, to provide flavor, facilitate food preservation, improve texture, or add other features deemed desirable.[51] Unintentional food additives are sometimes less easily identified, since they may occur as pesticides applied before harvesting, as materials that pass from wrappings into foods (*e.g.,* plasticizers), or from other inadvertent sources. Clearly, both intentional and unintentional additives warrant very careful study with consideration of both the biological activity of the contaminant and of the levels of contamination. Until the current time there has generally been little reason for serious concern that the additives will cause increased cancer risks at the levels of exposure known to occur. Some specific additives, often unintentional contaminants, have caused considerable concern, which may be inconsistent with the levels of contamination.[52] However, one example which demonstrated the importance of monitoring the biological activities of additives was the finding that 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2), a food preservative widely used in Japan for about 10 years, has strong mutagenic activity and moderate carcinogenic activity in rats and mice.[53] This demonstration led to a prompt ban on the further use of AF-2 in foods in Japan.

One of the most discussed of the intentional additives is saccharin.[54,55] At high levels saccharin appears to promote the development of cancers of the urinary bladder in rats and mice, but there is no evidence that saccharin can initiate tumors in experimental animals. Since the activity of tumor-promoters depends on their repetitive administration over relatively long periods and since the doses of saccharin required for promotion of urinary bladder tumor formation in rodents greatly exceed the amounts received by human populations that consume saccharin, the relevance of saccharin consumption to the development of cancer in the human has been strongly questioned. The results of epidemiologic studies on human populations have also provided very little support for a role of saccharin in the etiology of human cancer.[56,57]

A broader view of the multifaceted problem of the appropriate and safe use of food additives is beyond the scope of this review. Further information can be obtained from other sources.[50,51,58]

Mutagenicities of Foods or Food Components Without Demonstrated Carcinogenic Activity

In view of the concern for the safety of foods, the essential role of mutagenicity in the initiation of carcinogenesis, and the much greater ease of assessing mutagenic than carcinogenic activity, a wide variety of foods and chemicals present in foods have been assayed for mutagenic activity. Most of these foods and food chemicals have been assayed by the *Salmonella typhimurium* system devised by Ames and colleagues,[59] but a number of other bacterial, yeast, and mammalian cell culture systems have also been used.[60] These tests have provided a large amount of data which generally affirm the very low to undetectable mutagenic activity of many foods and food chemicals.[61,62] However, these studies also have shown mutagenic activity for some foods or chemicals contained in foods.[50,59–64] In many of the situations in which mutagenic activity was detected, the activities were so low that the source(s) of this activity were not characterized. In other cases, either natural constituents of the food or contaminants (*i.e.,* metabolites of microorganisms that infected the food, pesticide residues, or contaminants formed or added during processing or cooking) were identified as the source of mutagenicity. The mutagens that occur as natural constituents have a wide range of chemical structures, but especially prominent are phenols, quinones, aldehydes, and flavonoids.

The extrapolation of mutagenicity data to an estimation of the carcinogenic risks that these chemicals pose to humans is even more difficult than the extrapolation of risks for chemicals shown to be carcinogenic to animals. As discussed above, chemicals with carcinogenic or mutagenic activity are most frequently active as a result of metabolism to electrophilic derivatives. Other routes of metabolism in the animal convert these chemicals to nonmutagenic and noncarcinogenic metabolites (Fig. 1). To enhance the possibility of detecting a mutagen, mutagenicity assays usually contain a system for the metabolic activation of the chemical under test (for instance, by the addition of fortified liver microsomes). At the same time the mutagenicity assays lack the detoxification and excretory systems that provide the principal defense for the intact animal. Thus, the metabolic balance in the whole animal is frequently very different from that in the mutagenicity assay system, and a major fraction of the metabolites in the whole animal are generally removed from the tissues through excretory mechanisms. The multistage nature of carcinogenesis, of which only one stage is clearly a mutation event, further complicates the extrapolation of mutagenicity data for assessment of carcinogenic potential in the human.

The knowledge that a chemical contained in food has some mutagenic activity should not, of itself, be a cause for great concern. However, whenever a food chemical is shown to have moderate to strong mutagenic activity, the finding is an indicator that further examination of the situation is necessary. If the chemical or food is of only marginal value to the industry or consumers, its usage may be readily lowered or discontinued. In other cases, further data, including carcinogenicity assays *in animals*, determination of the levels of human exposure, and mechanistic studies, may be needed.

Perspectives

The current knowledge of carcinogens and their precursors that can occur in certain human foods provides a much improved basis for the assessment of the safety of food supplies. The need to protect populations from ingestion of aflatoxin B_1 and to reduce to the extent practical the intakes of N-nitroso compounds and of their precursors (especially nitrate and nitrite) is clear. On the other hand, the complete elimination from foods of all known and possible compounds with mutagenic and/or carcinogenic potential seems neither possible nor practicable.

Discussions of the possible hazard from carcinogens and mutagens in foods require reference to both the probable human exposures and the levels of activities of the chemicals. Overall, carcinogens with moderately potent activity in experimental animals or mutagens with moderate to high activity require more attention than those with weak activity. Furthermore, there is considerable agreement that chemicals that can initiate tumors (*i.e.*, those that are or are metabolized to electrophilic reactants) are of greater potential hazard at low doses than those that act only as tumor promoters. This differentiation is based on the finding that tumor promoters must be given repetitively to be effective and that their action is at least partially reversible. Finally, although it is not yet possible to assign "safety factors" for extrapolation of data for animals to humans, the likelihood of hazard to the human decreases with larger differences between the levels required for tumor induction in experimental animals and the human intakes. Constituents of foods that modify the responses of animals (and presumably of humans) to chemical carcinogenesis further complicate the extrapolation of data for calculating risks to humans. As described by Wattenberg[10] at these meetings, some naturally occurring constituents of foods, which have been called "anticarcinogens," reduce the incidences of tumors induced by a carcinogen. Although the mechanisms of action of the anticarcinogens are not fully explored, one important mode is through modification of the metabolism of a carcinogen so that more of it is converted to noncarcinogenic metabolites. Other naturally occurring constituents of foods, such as retinoids and selenium, appear to inhibit the promotion phase of carcinogenesis in some tissues.[65] On the other hand, high levels of fat intake can facilitate tumor promotion in some tissues.[66]

Further laboratory studies on the mutagenic, carcinogenic, and anticarcinogenic properties of specific food components and of mixtures will continue to provide information that can be used in maintaining the generally high safety of the food supplies in developed countries and in improving that of food supplies in developing countries. In favorable instances epidemiologic studies should add further understanding. Those epidemiologic studies that combine analyses for indicators of carcinogen intake (*e.g.*, urinary analyses of carcinogen metabolites or carcinogen adducts, analyses of adducts in susceptible tissues) with assessment of the likelihood of tumor development will be of particular importance.

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