Kirk-Othmer Encyclopedia of Chemical Technology.

FOOD TOXICANTS, NATURALLY OCCURRING

Food products are fundamentally mixtures of chemical compounds. That certain of these compounds may produce human toxicities has been known since before recorded history. Because human diets are normally composed of large numbers of different foods, only minute quantities of any specific toxic material are consumed. Thus dilution exerts a significant protective effect against acute intoxication. Toxicants are substances which, upon ingestion, produce changes in homeostasis that are threatening to the normal function of the organism. There are substantial differences in the toxicity thresholds of individuals to specific agents. Factors affecting toxicity include body weight, sex, age, general state of health, and the presence of potentiating or inhibitory substances. Some naturally occurring food toxicants are listed in Table 1 (1–11). Structures are shown in Figure 1. See also References 1 and 2.

1. Toxic Proteins, Peptides, Amides, and Amino Acids

Nitrogenous compounds are the most frequently implicated natural toxicants in foods. These compounds may be grouped either according to gross manifestations or specific structural characteristics. Accordingly, vitamin-destroying enzymes, hemagglutenins, enzyme inhibitors, and many hepatotoxins, are of protein, peptide, or amino acid composition. Many of the hepatotoxins are also carcinogens.

Enzyme inhibitors (qv) of a protein nature are of significant concern because of widespread occurrence. The most common of these affect the pancreatic enzymes, trypsin [9002-07-7] and chymotrypsin [9004-07-3], and are found in legumes, eg, soybeans, peas, most common beans, blackeyed peas, lupine, and khesari, as well as in egg whites and potatoes (3–9). Dozens of protein molecules of molecular weights of ca 15,000–30,000 are included in this group. Although the mode of action is difficult to characterize, these compounds form strong proteolysis-resistant complexes with their enzyme substrates, and consequently block trypsin and chymotrypsin activity. These compounds also enhance the production of amylase [9000-92-4] by the pancreas or at least stimulate its release by as much as 300%. This may be explained by the action of identified glycoprotein amylase inhibitors present in many legumes (10). Pancreatic hypertrophy, which has been hypothesized to produce increased secretion of cystine-rich enzymes, occurs and leads to a net loss of sulfur-containing amino acids from the body. These inhibitors also seem to block the feedback inhibition of pancreatic enzyme production which is normally based on intestinal concentration. Thus a cyclic and accelerating effect is produced whereby trypsin and chymotrypsin increase almost without limit, but their specific activities are blocked (11, 12).

Protein inhibitors are often active against a variety of enzymes, although each molecule may possess a separate and very distinct binding site for each enzyme. For example, many trypsin and chymotrypsin inhibitors are identical compounds (12).

Many protein inhibitors cause little nutritional difficulty because these compounds are heat labile under ordinary processing and cooking procedures including microwaving (13), and significant numbers are water soluble. Many are found in highest concentrations in the outer portions of plants, eg, wheat bran; thus normal peeling and milling operations also give some protection. It has been demonstrated that treatment with

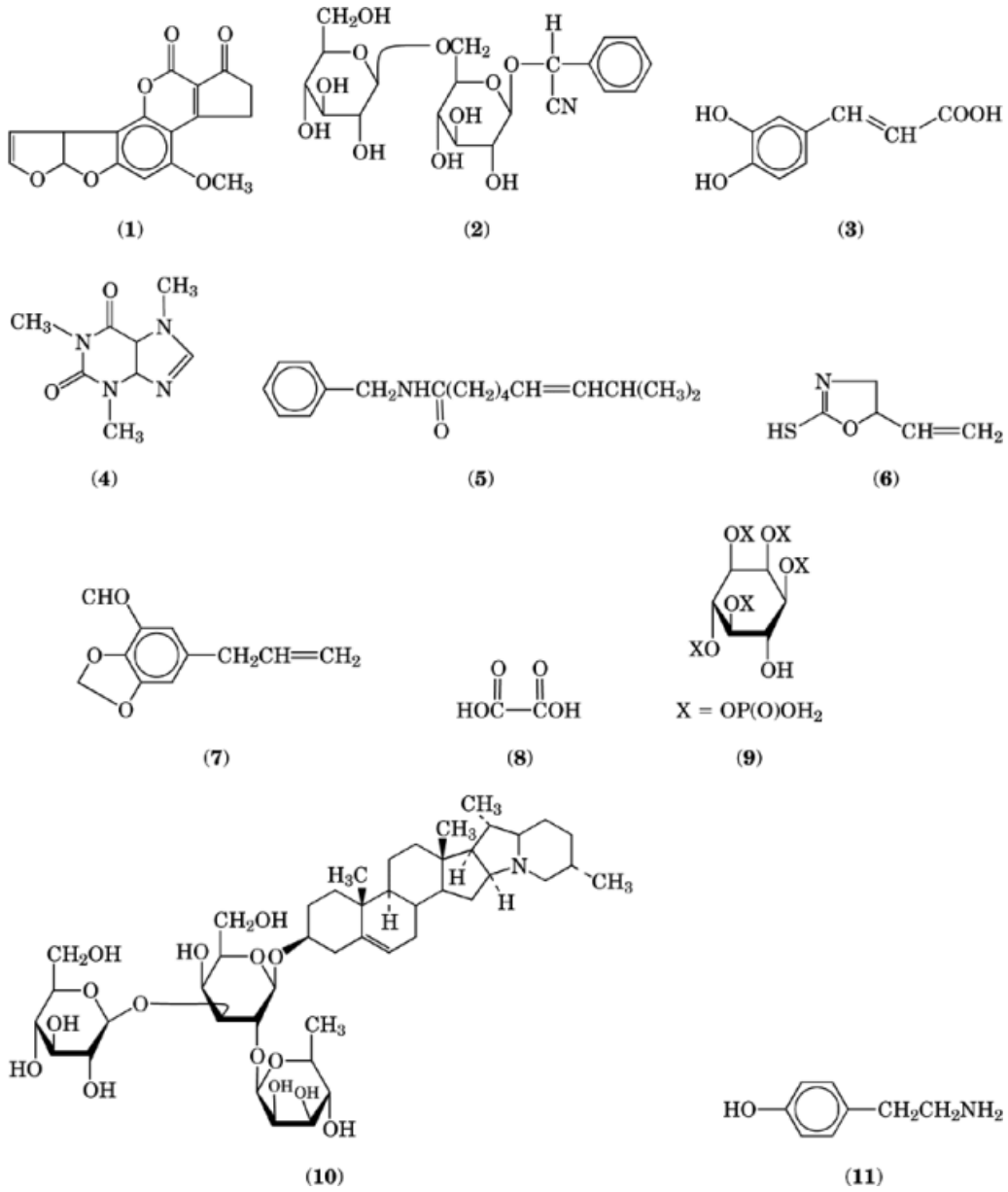


Fig. 1. Structures of naturally occurring food toxicants listed in Table 1.

compounds such as sodium sulfite [7757-83-7], ascorbic acid [50-81-7], and cupric sulfate [7758-98-7] (14, 15), as well as fermentation with *Rhizopus oligosporus*, such as in the production of tempeh, is also an effective means of reducing trypsin inhibitor activity in both fresh and hardened common beans (16).

Lupine seed, though used primarily in animal feeds (see Feeds and feed additives), does have potential for use in human applications as a replacement for soy flour, and is reported to contain both trypsin inhibitors and hemagglutenins (17). The former are heat labile at 90°C for 8 minutes; the latter seem much more stable to

Table 1. Naturally Occurring Food Toxicants

Compound	CAS Registry Number	Molecular formula	Toxin classification	Typical food sources	Structure number[a]
aflatoxin B_1	[1162-65-8]	$C_{17}H_{12}O_6$	mycotoxin	moldy grains, nut, oil seeds	(**1**)
amygdalin	[29883-15-6]	$C_{20}H_{27}NO_{11}$	cyanogenic glycoside	apricot pits, peach pits	(**2**)
avidin (chicken)	[1405-69-2]	[b]	forms insoluble complex within biotin	raw egg white	
caffeic acid	[331-39-5]	$C_9H_8O_4$	destroys thiamine	bracken fern	(**3**)
caffeine	[58-08-2]	$C_8H_{10}N_4O_2$	alkaloid, stimulant	coffee, tea, cola, nuts	(**4**)
capsaicin	[404-86-4]	$C_{18}H_{27}NO_3$	amide	*Capsicum* peppers	(**5**)
goitrin	[500-12-9]	C_5H_7NOS	goitrogen	cabbage, kale, onions, cress, cauliflower, broccoli, turnips	(**6**)
myristicin	[607-91-0]	$C_{11}H_{12}O_3$	alkaloid, psychoactive	nutmeg, mace, carrots	(**7**)
oxalic acid	[144-62-7]	$C_2H_2O_4$	reacts with calcium to reduce availability	rhubarb	(**8**)
phytic acid	[83-86-3]	$C_6H_{18}O_{24}P_6$	reacts with calcium to reduce availability	oats	(**9**)
solanine	[20562-02-1]	$C_{45}H_{73}NO_{15}$	glycoalkaloid, antiacetylcholinesterase	potatoes, tomatoes, apples, eggplant	(**10**)
thiaminase	[9030-35-7]	[c]	enzyme, inactivates thiamine	raw fish	
tyramine	[51-67-2]	$C_8H_{11}NO$	vasoactive amine	cheeses, bananas, plantains, tomatoes, pineapple	(**11**)

[a] See Figure 1.
[b] Mol wt ca 60,000.
[c] Mol wt ca $(75 - 100) \times 10^3$.

normal cooking temperatures. Various tropical root crops, including yam, cassava, and taro, are also known to contain both trypsin and chymotrypsin inhibitors, and certain varieties of sweet potatoes may also be implicated (18).

Reports of specific amino acid toxicities from normal eating patterns are rare (see Amino acids). Capsaicin (**5**), the amide responsible for the pungency of *Capsicum* peppers, is highly irritating at concentrations of 1:1,000,000 and highly toxic when taken in large doses (19). Of the essential amino acids, methionine [63-68-3] seems the least tolerated, especially on restricted protein intakes, where toxic doses have been reported in the range of 10–46 g/d (14). Tyrosine [60-18-4] behaves similarly, and both result in hepatic and neurological lesions when fed to rats at toxic levels. Leucine [61-90-5] has been responsible for depressed nicotinamide adenine dinucleotide (NAD) synthesis at levels of 14–20 g/d, whereas the toxicity of lysine [56-87-1], which causes abdominal cramps and diarrhea, occurs only with dose levels in excess of 64 g/d (20).

Of the nonessential amino acids, glycine [56-40-6] may be responsible for isolated toxicities at high (>30 g/d) dosages but is nonetheless generally considered nontoxic. Recognition of the Chinese Restaurant Syndrome in 1968 stimulated interest in the toxicity of glutamic acid [617-65-2], particularly as monosodium glutamate (MSG). Numbness in the back and neck, weakness, palpitation, and other evidence of neurological block have been observed in susceptible individuals with intakes of 3–25 g/d of MSG. Commercial and restaurant use of MSG has since been significantly reduced; however, these effects are closely related to L-glutamic acid [56-86-0] intolerance, and remain of interest because many native proteins contain 30% or more of this amino acid. Although all amino acids except alanine [56-41-7] have been shown to be toxic, the probability of intoxication is very remote. Humans seem able to tolerate all amino acids in excess of 10 times the recommended intake.

Lathyrus sativus (khesari), which constitutes a principal food crop for many in India, has been known for decades to cause neolathyrism. The causative agent, *N*-oxalyl-L-α-diaminopropionic acid (ODAP), produces

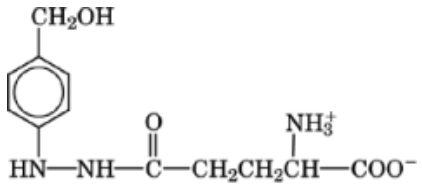
partial or total loss of control of the lower limbs with associated neurological symptoms (21). Common methods of preparation, including soaking in lime water and boiling, are effective in destroying this amino acid.

The seeds of legumes may contain hemagglutenins and lectins that may cause destruction of the epithelia of the gastrointestinal tract; interfere with cell mitosis; cause hemorrhage; impede renal, cardiac, and hepatic function; and produce red blood cell agglutination (22). Many of these compounds are rendered inactive by moist heat, and the toxicity may be further reduced or neutralized by digestive enzymes, making them poorly absorbed. Because lectins reach the colon mostly in an inactive state, they appear to protect humans from colon cancer by causing hypersecretion of intestinal mucus, or by direct toxic effect on tumor cells (23).

Saponins disrupt red blood cells and may produce diarrhea and vomiting. They may also have a beneficial effect by complexing with cholesterol [57-88-5] and thus lowering serum cholesterol levels (24, 25). In humans, intestinal microflora seem to either destroy saponins or inactivate them in small concentrations.

Acute toxicoses resulting from consumption of toxic mushrooms is infrequent, yet of increasing concern because of the practice of gathering fungi in the wild. The most serious of these toxicoses result from the Amanita family of mushrooms which contains several toxic peptides belonging to the amatoxin and phallotoxin groups. Of increased concern to 1990s toxicologists is the upsurge in reported cases of Amanita identification and poisonings in areas previously thought to be Amanita free. Whether these toxic species have always inhabited these environs or have been more recently introduced remains uncertain. Other toxic fungi also contain an array of hepatotoxic peptides and hallucinogens, some having been utilized for their drug effects by Native Americans for centuries. Most of these reactions are associated with progressive hepatic degeneration, and although only a few are fatal, their treatment is normally only symptomatic.

Both the common cultivated mushroom as well as the Shitake mushroom contain hydrazines that have been shown to be carcinogenic precursors in experimental animals. *Agaricus bisporus*, the primary commercial mushroom in the United States, contains the hydrazine analogue agaritine [2757-90-6] **12**. Agaritine forms 4-hydroxymethylphenylhydrazine which can be transformed *in vitro* to 4-methylphenylhydrazine (4-MPH), the first hydrazine shown to be carcinogenic (26). Agaratine is destroyed by moist heat, and 4-MPH has not been isolated itself in mushrooms (27). Hence, toxic significance in the human diet remains unproven. In extreme cases, 100 g/d of fresh mushrooms approximates the carcinogenic dose observed in animals. Hydrazine levels, however, vary considerably as a function of variety, processing, storage, and preparation. One week of refrigerated storage reduces levels significantly, and all hydrazines are lost during canning and/or cooking (28, 29) (see also Hydrazine and its derivatives).



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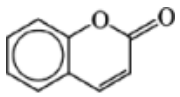
2. Phytoalexins

Phytoalexins are low molecular weight compounds produced in plants as a defense mechanism against microorganisms. They do, however, exhibit toxicity to humans and other animals in addition to microbes (30). Coumarins, glycoalkaloids, isocoumarins, isoflavonoids, linear furanocoumarins, stilbenes, and terpenes all fall into the category of phytoalexins (31). Because phytoalexins are natural components of plants, and because

their concentration may increase as a response to production and management stimuli, it is useful to recognize the possible effects of phytoalexins in the human diet.

Linear furanocoumarins are potent photosensitizing agents in celery, parsley, parsnips, limes, and figs. The most commonly reported symptoms include contact dermatitis and photodermatitis, particularly on the hands and forearms (32, 33). Many linear furanocoumarins are present in these plant materials, all seem stable to cooking temperatures, and a few have even been reported to be mildly mutagenic (34). Coumarin **13** and its derivatives are also present in many species of citrus, occurring primarily in the peel, and hence find their way into human diets largely through the use of cold-pressed citrus-peel oils which are used as flavoring agents (35). Whereas both linear furanocoumarins and coumarins are widely distributed and possess toxic properties, reported cases of human toxicity have been limited largely to contact dermatitis in individuals handling large quantities of plants containing these compounds. The chronic low level consumption of these two classes of compounds, as would occur in a normal varied diet, has not been conclusively associated with human illness.



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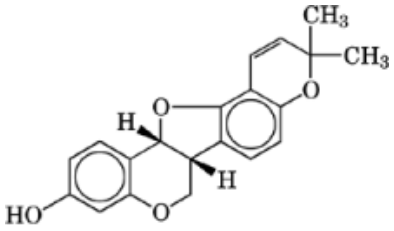


(**14**)

Other common phytoalexins in food materials are pisatin, cinnamylphenols, glyceolin, phaseolin [13401-40-6] **14**, and 5-deoxykieritol in peas, beans, soybeans, and lima beans; viniferin in grapes; momilactones and oryzalexins in rice; α-tomatine in tomato; lubimen in eggplant; and capsidiol in green peppers.

Enumerable phytoalexins, including furanosesquiterpene, ipomeamarone, eudesmanes, and others, have been isolated from mold-infected sweet potatoes (31). The clinical symptoms seem to revolve around lung edema (36). Whereas high concentrations of these chemicals can occur in damaged sweet potatoes, the occurrence is much less (by as much as 20-fold) in nondamaged sweet potatoes (37). Of possible concern to human health is the fact that blemishes sufficient to result in large increases in concentration of lung-edema toxins are not always easily detected by the naked eye. Additionally, these compounds are heat stable (38).

3. Oligosaccharides

Oligosaccharides, specifically the α-galactosides raffinose [512-69-6], stachyose [470-55-3], and verbascose [546-62-3], are widely present in legumes and are indigestible by humans because of a lack of α-galactosidase. As a result, these compounds undergo fermentation in the colon with the concomitant production of CO_2, H_2, and CH_4, commonly referred to as flatulence. Reports have shown germination to be effective in reducing α-galactoside content of cowpeas and other legumes (39, 40).

Goitrogens are compounds that produce goiter by interfering with thyroxine synthesis in the thyroid gland. Foodborne goitrogens are often characterized by the presence of sulfur and most are thiocyanates or closely related compounds. Because of their widespread occurrence in Cruciferae, eg, cabbage, kale, onions, cress, broccoli, cauliflower, rutabaga, turnip, and radish, goitrogens are among the most common and longest recognized substances of toxic nature in the human food supply (41). Thiocyanates actively compete with iodine for the same binding sites on the tyrosine molecule. Examples of goitrogenic compounds, other than thiocyanates, are derivatives of 2-3*H*-thioxazolidinone, found in watercress and mustard; 5-phenyl-2-thioxazolidinone in watercress; and L-5-vinyl-2-thioxazolidinone in cabbage and kale. It has also been demonstrated that the quantity of the precursor found in plant materials seems related to available sulfur in the soil (42). However, studies on thioglucoside concentration in rutabaga have demonstrated no difference between roots grown on low S soils as compared to those grown over coal-fly ash (43). The enzyme responsible for the conversion of the precursor into the active molecule is destroyed by the heat associated with normal cooking operations (44).

4. Oxalates, Phytates, and Other Chelates

Of nutrient chelates in the human diet, oxalates and phytates are the most common. Oxalic acid (**8**), found principally in spinach, rhubarb leaves, beet leaves, some fruits, and mushrooms, is a primary chelator of calcium. Oxalate present in pineapple, kiwifruit, and possibly in other foods, occurs as calcium oxalate [563-72-4], CaC_2O_4. This compound is in the form of needle-like crystals, known as raphides, which can produce painful sensations in the mouth when eaten raw (45). The effects of oxalic acid in the diet may be twofold. First, it forms strong chelates with dietary calcium, rendering the calcium unavailable for absorption and assimilation. Secondly, absorbed oxalic acid causes assimilated Ca to be precipitated as insoluble salts that accumulate in the renal glomeruli and contribute to the formation of renal calculi (46).

Phytic acid (**9**), although restricted to a more narrow range of food products, mainly grains, complexes a broader spectrum of minerals than does oxalic acid. Decreased availability of P is probably the most widely recognized result of excessive intakes of phytic acid, yet Ca, Cu, Zn, Fe, and Mn are also complexed and rendered unavailable by this compound (47–49). Phytic acid has also been reported to reduce the activity of α-amylase and to decrease the activity of both proteolytic and lipolytic enzymes (50).

In addition to these purely nutritional effects, dietary chelates, especially oxalic acid, may produce more classic toxicity when ingested in excessive quantities. Although there is no doubt that intakes of 5 g or more of oxalic acid could be fatal to humans, the probability of such ingestion is remote. The consumption of some 4 kg of rhubarb leaves or roughly twice that quantity of spinach would be required. Therefore, concern regarding the possible hazardous effects of ingesting plant foods containing oxalate seems unwarranted. High intakes of both calcium and vitamin D help to offset the deleterious effects of oxalates (see Vitamins).

4.1. Vasoactive and Psychoactive Amines and Alkaloids

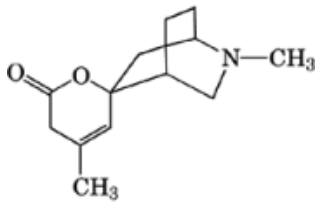
Most compounds producing hypertensive episodes are classified as amines and are found in greatest concentration in banana, plantain, tomato, avocado, pineapple, broad beans, and various cheeses. Amines that are vasoactive include dopamine [51-61-6], $C_8H_{11}NO_2$; tyramine (**11**); histamine [51-45-6], $C_5H_9N_3$; tryptamine [61-54-1], $C_{10}H_{12}N_2$; noradrenaline [51-41-2], $C_8H_{11}NO_3$; and dihydroxyphenylalanine [59-92-7] (DOPA), $C_9H_{11}NO_4$ (51).

Patients receiving monoamine oxidase inhibitors (MAOI) as antidepressant therapy have been especially subject to the hypertensive effects of vasoactive amines (52). These dietary amines have also been implicated as causative agents in migraine. Other naturally occurring alkaloids (qv) have been recognized for centuries as possessing neurological stimulant and depressant properties.

Caffeine (**4**), a xanthine derivative, has been consumed for thousands of years and is present in over 60 plant species including coffee (qv) beans, tea (qv) leaves, cacao beans (see Chocolate and cocoa), and cola

nuts. In addition to naturally occurring sources, caffeine has been used as a food ingredient (flavoring) for over 100 years. Caffeine is rapidly and completely absorbed, being distributed quickly throughout the body with no so-called barriers to limit absorption or distribution. Compounding this rapid absorption is the fact that caffeine is inefficiently excreted by the kidneys. Caffeine produces stimulatory effects by facilitating mental and muscular effort and diminishes drowsiness and fatigue. It has been suggested that these effects may be the result of caffeine acting as an antagonist of adenosine in respiratory, renal, and neural cardiovascular tissues (53). Individual thresholds of toxicity vary considerably, but symptoms such as restlessness, increased respiration, muscular tension and twitching, and tachycardia may imply acute toxicity. Although caffeine content in beverages is quite variable, 20 cups or more of coffee per day (85–100 mg/cup) would be necessary in most individuals to approach acute toxicity, and the human fatal dose has been estimated at about 10 g (150–200 cups of coffee) in a 24 h period. Considered a stimulant in usually encountered doses, caffeine's acute toxicity may actually be depressant in character (54, 55).

Depressant symptoms, which include burning abdominal pain, decreased excitability, convulsions, nausea, and coma, become the general syndrome for all oral alkaloid poisoning. Discorine [3329-91-7] **15**, a γ-unsaturated lactone found in yams, is an alkaloid having the empirical formula $C_{13}H_{21}O_2N$; it has been isolated from Nigerian yams, thus establishing the discorine-type alkaloids as representative of the *Dioscorea* genus of plants (56). Seeds of *Senecio* contain alkaloids belonging to the pyrrolizidine group and, in addition to producing characteristic signs of alkaloid toxicity, these are suspected of being hepatic carcinogens. Ergotism is the disease caused by intoxication by one of at least twelve alkaloid derivatives of lysergic acid produced by a parasitic fungus (ergot) on grains. Myristicin (**7**), found in both nutmeg and mace, is a psychoactive agent that may be fatal in infants who consume as little as two whole nutmegs. Its toxicity resembles alcohol intoxication.



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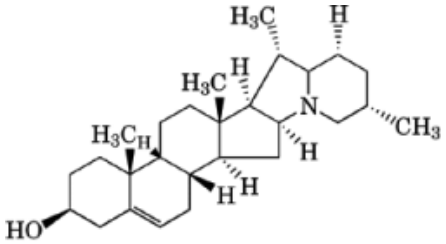

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Several glycoalkaloids present in food are of toxicological interest. Solanine (**10**), found in potatoes, tomatoes, apples, eggplant, and sugar beets, has been responsible for several cases of moderate to severe poisoning. Solanine is a cholinesterase inhibitor (see Choline), and toxic doses are probably ca 200 mg. Market potatoes contain about 1–5 mg of solanine per 100 g fresh weight. The USDA establishes solanine levels of 20 mg/100 g as the limit for safe consumption. Because the greatest proportion of solanine occurs in the skin and eyes of potatoes, the practice of peeling diminishes the intake of this alkaloid. However, the increased consumption of potato skins as snack items has resulted in increased glycoalkaloid intake in some individuals.

Toxic symptoms include headache, nausea, and diarrhea. Solanine is poorly absorbed, rapidly excreted, and readily hydrolyzed to the less toxic solanidine [80-78-4] **16** in the intestinal tract. Lethal concentrations are estimated at about 3 mg/kg body weight (57, 58).

Many studies have reported a link between consumption of sunburned potatoes, ie, those exposed to the sun and having an accumulation of chlorophyll and solanine under the skin, with incidences of teratogenic effects and even death (59–61). Because sunburned potatoes in the commercial marketplace are relatively rare, and because the long-term effects of consumption of potatoes at the maximum established limits of solanine concentration are uncertain, there is equal uncertainty of the true incidence of human toxicity (62).

Solasodine [126-17-0], $C_{27}H_{43}NO_2$, a spirosalane alkaloid, is found in eggplant, and has been reported to be teratogenic in hamsters (63), but not in rats (64). Toxicity in humans has not been reported. Tomato products contain α-tomatine, a steroidal glycoalkaloid which has been reported to be toxic to a wide range of organisms, including microorganisms, cattle, and mice (65). Most of the glycoalkaloids occurring in plant materials exert a natural pesticidal function. It has been estimated that consumption of natural pesticides is some 10,000 times greater than consumption of manufactured ones (66).

5. Antinutrients

Any substance that destroys, inactivates, or in other ways renders unavailable an essential dietary constituent can be termed an antinutrient. The most widely studied are antivitamins. The presence of antivitamins in certain foods means that merely assuring an adequate intake of a vitamin is no guarantee that a deficiency state cannot exist physiologically. The enzyme thiaminase acts by either specific splitting of the thiamine molecule or nonspecific hydrolysis (67). Niacin inhibitors, acting through nicotinamide mononucleotide (NMN) depression in erythrocytes, have been studied in corn and millet, and a biotin antagonist, avidin, has long been recognized in raw egg white. Avidin forms a stable complex with biotin, thus rendering the vitamin unavailable for metabolic reaction (68). Linatine [10139-06-7], found in flaxseed, is the only pyridoxine antagonist known and seems to function by the formation of a stable complex (69). Yeast and pea seedlings contain specific pantothenic acid antagonists, although the structure and mode of action are unexplained (70). Riboflavin antagonism, found only in the Akee plum of Jamaica, is rather rare, but is of interest because it can be fatal (71).

Many plant substances possess antivitamin D activity but the mode of action and in most cases the identity remain unknown. Rachitogenic factors have been observed in yeast. Because of the metabolic interrelationships that exist between vitamin D, Ca, and P, it is sometimes difficult to differentiate between chelators of mineral elements and true antivitamins. One reported vitamin D antagonist in oats was later identified as phytic acid (72).

The antagonisms that exist between unsaturated fatty acids, and carotene and vitamin E are complicated and largely undefined. Linoleic acid acts as an antivitamin to *dl*-α-tocopherol [59-02-9, 1406-18-9, 10191-41-0] (vitamin E) by reducing availability through direct intestinal destruction. Various lipoxidases destroy carotenes and vitamin A (73). Dicoumarol [66-76-2] (3,3′-methylenebis(4-hydroxycoumarin)) is a true antimetabolite of vitamin K [12001-79-5] but seems to occur only in clover and related materials that are used primarily as animal feeds (74).

At various times, antivitamin factors specific to vitamin B_{12}, folic acid, and choline have been reported. However, it is uncertain whether these are true antimetabolites or if they may result from metabolic interrelationships with other dietary constituents.

Investigations have focused on the content of polyphenolics, tannins, and related compounds in various foods and the influence on nutrient availability and protein digestibility. It has been established that naturally occurring concentrations of polyphenoloxidase and polyphenols in products such as mushrooms can result

in reduced iron bioavailability (75). Likewise, several studies have focused on decreased protein digestibility caused by the tannins of common beans and rapeseed (canola) (76–78).

6. Vitamin Toxicity

Reported cases of vitamin toxicity owing to overdose are usually associated with increased over-the-counter availability of supplemental vitamins and indiscriminate supplementation. The misconception that if a little is good a lot is better has compounded toxicological problems with the vitamins. Fat-soluble vitamins tend to accumulate in the body with relatively inactive mechanism for excretion and cause greater toxicological difficulties than do water-soluble vitamins.

Infants may be sensitive to doses of vitamin A [11103-57-4] in the range of 75,000–200,000 IU (22.5–60 mg), although the toxic dose in adults is probably 2–5 million IU (90.6–1.5 g). Intakes in this range from normal food supplies without oral supplements are simply beyond imagination (79). Vitamin D [1406-16-2] toxicity is much more difficult to substantiate clinically. Humans can synthesize active forms of the vitamin in the skin upon irradiation of 7-dehydrocholesterol. Toxic symptoms are relatively nonspecific, and dangerous doses seem to lie in the range of 1000–3000 IU/kg body wt (25–75 μg/kg body wt) (80). Cases of toxicity of both vitamins E and K have been reported, but under ordinary circumstances these vitamins are considered relatively innocuous (81).

Of the water-soluble vitamins, intakes of nicotinic acid [59-67-6] on the order of 10 to 30 times the recommended daily allowance (RDA) have been shown to cause flushing, headache, nausea, and moderate lowering of serum cholesterol with concurrent increases in serum glucose. Toxic levels of folic acid [59-30-3] are ca 20 mg/d in infants, and probably approach 400 mg/d in adults. The body seems able to tolerate very large intakes of ascorbic acid [50-81-7] (vitamin C) without ill effect, but levels in excess of 9 g/d have been reported to cause increases in urinary oxalic acid excretion. Urinary and blood uric acid also rise as a result of high intakes of ascorbic acid, and these factors may increase the tendency for formation of kidney or bladder stones. All other water-soluble vitamins possess an even wider margin of safety and present no practical problem (82).

7. Essential Minerals and Heavy Trace Elements

Ingestion of at least 10 times normal levels of essential minerals would be required to approach toxic proportions (see Mineral nutrients). The only exceptions occur in cases of plant foods grown on soils unusually high in Mo [7439-98-7], Se [7782-49-2], and Cu [7740-50-8]. Levels can reach toxic quantities in these cases, but these are rare occurrences.

Cases involving human toxicity from heavy trace elements, such as Pb [7439-92-1], Hg [7439-97-6], As [7440-38-2], and Cd [7440-43-9], are much more common but are almost exclusively traced to accidental contamination rather than true natural occurrences. Consumption of seafoods taken from waters where industrial pollution raised mercury levels has been responsible for some reported cases of mercury poisoning. Methylmercury acetate [108-07-6] seems to be the toxic compound of most interest to humans and is formed primarily from microbial action. Infrequent problems with lead and cadmium have been traced to steels and equipment containing these elements coming in contact with foods during handling or processing (see Food processing). Naturally high levels of arsenic have been reported in some crustaceans and fishes, yet food problems have been restricted to meats taken from livestock treated with arsenic-containing antibiotics (83) or to accidental contamination (see Meat and meat products).

Heavy metals are of importance in human toxicity because the body possesses only inactive mechanisms for their excretion; thus chronic, low level intakes can accumulate to toxic proportions. Treatment has likewise

been relatively unsuccessful, except for symptomatic relief. No effective means has been discovered to increase excretion.

8. Cyanogenic Glycosides

Complex glycosides, which upon hydrolysis yield hydrogen cyanide [74-90-8], are commonly found among plant materials. The toxicity of this class of compounds, found in the bitter almond, pits of stone fruits, sorghum, and lima beans, is directly related to HCN liberation upon digestive hydrolysis. Amygdalin (**2**), the cyanogenic glycoside of apricot pits, has been promoted as both a cancer cure and a vitamin. However, it has never been associated with a medically verified cancer cure, and no trained nutritionist recognizes the compound as a vitamin. Indeed, many cases of poisoning, and even death, have been ascribed to its use. Approximately 50 apricot pits contain a fatal dose of amygdalin (84).

The cyanogenic glycosides, phaseolunatin [554-35-8], $C_{10}H_{17}NO_6$, and vicianin [155-57-7], $C_{19}H_{25}NO_{10}$, have been isolated from lima beans and vetch, respectively. Several studies have reported that heating (cooking) acts to decrease the quantity of HCN liberated by these compounds upon enzymatic hydrolysis.

9. Nitrates, Nitrites, and Nitrosamines

The carcinogenicity of nitrosamines has created widespread concern over the safety of food products that are significant sources of nitrates and nitrites. Nitrosamines are readily formed by reaction of secondary amines with nitrites at acid pH, conditions which may occur in the gastrointestinal tract.

Nitrates are found in fairly high concentrations in beets, spinach, kale, collards, eggplant, celery, and lettuce. Additionally, nitrates and nitrites are commonly used in the curing solutions of bacon, ham, and other cured meats. In cured meats, nitrates and nitrites control the growth of microorganisms, particularly *Clostridium botulinum*, and also serve as color preservatives.

Although the potentially carcinogenic nitrosamines may be present in foods, particularly cured meats, occurrence is infrequent and at low levels. USDA regulations stipulate that ascorbic acid be added to cured meats at five times the level of nitrates and nitrites to prevent the formation of carcinogenic *N*-nitroso compounds (see Food additives). Nitrosamines vary widely in molecular structures, and some 100 or more may be capable of producing pathological effects. Most are specific hepatotoxins, producing hepatic parenchymal cell necrosis, and may also act in a synergistic capacity with other carcinogens, notably the polycyclic hydrocarbons (85).

10. Sodium Chloride

Sodium chloride [7647-14-5] is an essential dietary component. It is necessary for proper acid–base balance and for electrolyte transfer between the intra- and extracellular spaces. The adult human requirement for NaCl probably ranges between 5–8 g/d. The normal diet provides something in excess of 10 g/d NaCl, and adding salt during cooking or at the table increases this intake.

Excessive intake of NaCl contributes to increased fluid retention and there may be a relationship between NaCl intake and hypertension. Few topics have caused such debate among nutritionists and physicians. There is no doubt that the relationship between hypertension and NaCl intake is of significance when compounded by obesity, or in about 30% of hypertensives. Edema resulting from excessive salt intake, especially in relatively inactive persons, is a principal contributing factor in elevated blood pressure. Both consumers and food processors have reduced use of NaCl.

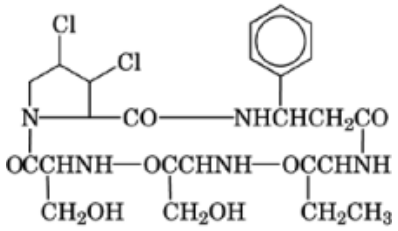
11. Toxins

11.1. Mycotoxins

The condition produced by the consumption of moldy foods containing toxic material is referred to as mycotoxicosis. Molds and fungi fall into this category and several derive their toxicity from the production of oxalic acid, although the majority of mycotoxins are much more complex.

Mycotoxins find their way into the human diet by way of mold-contaminated cereal and legume crops, meat, and milk products. Corn and peanuts probably represent the most common sources of mycotoxins in the human diet. Many mycotoxins are acutely toxic as well as being potent carcinogens (86).

Many parasitic fungi have been shown to produce toxins; however, the toxins of *Aspergillus* and *Penicillium* have perhaps the greatest potency against humans. Polycyclic peptides are among the most dangerous toxic compounds produced by fungi. A number of mycotoxins contain the diketopiperazine nucleus and all are composed of amino acid units. Islanditoxin [10089-09-5], $C_{24}H_{31}Cl_2N_5O_7$ **17**, produced by *Penicillium islandicum* on rice and other grains, is a Cl-containing bicyclic peptide which includes α-aminobutyric acid [80-60-4], $C_4H_9NO_2$, β-phenyl-β-aminopropionic acid [13921-90-9], $C_9H_{11}NO_2$, serine [56-45-1], $C_3H_7NO_3$, and dichloroproline [60548-67-6], $C_5H_7Cl_2NO_3$. Several anthraquinone derivatives, produced by members of the *Penicillium* group, are also of toxicological interest. Examples are skyrin [602-06-2], $C_{30}H_{18}O_{10}$, luteoskyrin [21844-44-6], and iridaskyrin [568-42-3], $C_{30}H_{18}O_{10}$. Various mycotoxins also include alkaloids and xanthones, coumarin, and terpene derivatives. Some are thermolabile, others thermostable. The latter are of greatest importance in food products because routine processing and cooking do little to reduce their potential toxicity. Toxic metabolites are usually produced only after mycelia have become established in the substrate. For this reason, foods are usually free of toxins until such mycelial development occurs (87). The mode of action of mycotoxins varies according to chemical nature. Some act by blocking cell-wall synthesis, by disrupting membrane integrity, or by decoupling oxidative phosphorylation and inhibiting respiratory pathways. Others are chelates that inhibit synthesis of proteins or DNA.



(17)

Aflatoxins, first noted as metabolites from *Aspergillus flavus*, are also produced by *A. parasiticus*, *A. niger*, *A. ruber*, *A. ostinaus* Wehmer, *A. wentii*, *A. vesicolor*, *Penicillium puberculum*, *P. citrium*, *P. variable*, and *P. frequentans*, as species of *Rhizopus*. *Aspergillus flavus* is a common contaminant of a multitude of foods, including soybeans, groundnuts, cassava, peas, pears, cacao pods, Brazil nuts, pecans, millet, corn, and wheat. Because of this widespread occurrence on plant materials the rare isolation of aflatoxins in food products is not surprising (88).

The term aflatoxin is not compound-specific. Different toxic compounds have been designated as B_1 and G_1 [1165-39-5], and B_2 [7220-81-7] and G_2 [7241-98-7] (dihydro derivatives of B_1 and G_1), as well as M_1 [6795-23-9], M_2 [6885-57-0], P_1 [32215-02-4], GM_1 [23532-00-5], and B_3 [23315-33-5]. Aflatoxin B_1 (**1**) is of greatest occurrence in nature, followed by G_1, B_2, and G_2. Water content of medium, temperature, pH, and light are among those environmental factors that affect aflatoxin production.

Aflatoxin B_1, produced by *Aspergillus flavus*, is probably the most potent hepatocarcinogen found in nature (89). Measurable levels of aflatoxin residues have been found in U.S. cereal grains and peanuts. These compounds seem resistant to cooking and processing (90, 91); hence ordinary methods of preparation do not limit their intake. Because carcinogens may take many years to be recognized as causing illness, the real implication of aflatoxin ingestion in normal human diets is uncertain (92).

Acute toxicoses, as well as potential long-term effects of aflatoxin ingestion, have been extensively reported (93). Autopsy reports have noted a positive correlation between aflatoxin B_1 and victims of Reye's Syndrome in Thailand (94), but this evidence should only be considered as suggestive and preliminary (95).

Intoxication by aflatoxins is referred to as aflatoxicosis. Edema and necrosis of hepatic and renal tissues seem characteristic of aflatoxicosis, and hemorrhagic enteritis accompanied by nervous symptoms often appear in experimental animals. The mode of action of aflatoxins involve an interaction with DNA and inhibition of the polymerases responsible for DNA and RNA synthesis (96).

Cereals, bakery products, and oilseed products are those foods that are of highest risk in regard to aflatoxin contamination (see Wheat and other cereal grains). One study showed 74% of peanut butter samples to contain aflatoxins (97) (see Nuts). Another study (31) suggests a possible link of aflatoxin ingestion with mental retardation, but this connection remains largely uncorroborated. Specific links between liver carcinoma and aflatoxin ingestion have not been substantiated fully, and it is probable that only minimal dangers are to be encountered from commercially processed foods.

Many procedures have been studied for detoxification of aflatoxins, including heat and treatment with ammonia, methylamine, or sodium hydroxide coupled with extraction from an acetone–hexane–water solvent system. Because in detoxification it is important to free the toxin from cellular constituents to which it is bound, a stabilization of proteins using a tanning compound such as acetaldehyde (qv) or glutaraldehyde may be a solution to the problem (98).

11.2. Seafood Toxins

Virtually scores of fish and shellfish species have been reported to have toxic manifestations. Most of these toxicities have been shown to be microbiological in origin. There are a few, however, that are natural components of seafoods.

Several species of the moray eel (*Gymnothorax*) have caused toxic reactions, especially in Japan. The toxic principle appears to be proteinaceous and is found predominately in the blood but it may occur in the flesh as well. Its exact structure remains somewhat uncertain.

Amnesic shellfish poisoning resulted in four deaths in northeastern Canada in the early 1990s, and domoic acid, the causative agent, was first documented on the Washington and Oregon coasts in 1991. The toxin is produced by a single-celled phytoplankton that constitutes part of the food chain of some shellfish, including Dungeness crab. Domoic acid is concentrated in the tissues of these shellfish, and upon ingestion can result in symptoms including memory loss (hence the name of the condition), and in large doses, ultimately death. Domoic acid is not affected by common methods of food preparation and no medical treatment is presently available for acute poisoning (99).

Pufferfish toxin, isolated from a dozen or more species, has been identified as having the empirical formula $C_{11}H_{17}N_3O_8$, but the structure is not well-established, nor is it certain that the same structure is universally responsible for poisoning, although this is assumed to be the case. The so-called paralytic shellfish poisoning reported in many areas of the world has a microbiological etiology, and is thus more accurately a contamination rather than a natural toxicosis. The paralytic effects of the poisoning begin as a tingling sensation in the lips, tongue, and extremities, and gradually progress into nausea and convulsions. Japanese statistics indicate mortality rates approaching 65% (100).

The liver of sharks and other oily fishes sometimes accumulate toxic levels of vitamin A, and cases of acute poisoning have been reported both among Eskimos and the Japanese.

11.3. Other Toxins

Some consumers have become concerned over the possible toxicity of free radicals in lipid oxidation products, including degradation products of cholesterol, in food fats and oils. Whereas complicated autoxidation and polymerization of fats does occur at temperatures of 200–300°C, such conditions are rarely encountered in normal cooking. Toxicity of these degradation products in experimental animals has been reported only using excessively large doses and presents no hazard to human health under ordinary circumstances. Free radicals resulting from lipid degradation are extremely short-lived (nanoseconds), and thus consumption is unlikely. Accordingly, free radicals from food possess no known toxicological significance (101).

Cyasin, a component of the nut of the cycad tree, a native of tropical environs, produces an acute toxicity in addition to drastically increasing the incidence of Lou Gerhig's disease (amyotropic lateral sclerosis). Cyasin is carcinogenic (102).

Estrogens are ingested by humans from both plant (cereal grains, legumes, potatoes, carrots, parsley, tree fruits, yams, vegetable oils) and animal (liver, egg yolk) sources. Whereas estrogens are known to promote tumor growth, the activity of food estrogen is one-tenth to one-thousandth the level of the most common human circulating estrogen. There has been no implication of foodborne estrogen in the etiology of human cancer, but the effects of long-term subphysiological intakes remain unclear (103). Some studies have concluded that because phytoestrogens are not mutagenic, they may be tumor promoters rather than tumor initiators (104).

A toxic component of braken fern, perhaps either quercetin (105) or ptaquiloside, a glucoside (106), has a mixed history of carcinogenicity. It is sometimes implicated in an increased incidence of bladder cancer in animals and esophageal cancer in humans. Multiple other dietary components seem to either promote or interfere with its action, and the significance of braken fern in human carcinogenesis remains unproven.

Halogenated compounds, found in high concentrations in seaweeds consumed in Japan and Hawaii, have been suspected of being carcinogenic, largely based on epidemiological extrapolation (high incidences of hepatic carcinoma). However, direct human causation has not been established (107).

Urethane [51-79-6] (ethyl carbamate) occurs as a natural by-product in fermented products such as wine, liquors, yogurt, beer, bread, olives, cheeses, and soy sauces. Whereas urethane has a known cancer etiology in experimental animals, no such relationship has yet been proven in humans (108, 109). Alcohol may act by blocking the metabolism of urethane, and thus exert a protective effect in humans consuming alcoholic beverages (110).

Polycyclic aromatic hydrocarbons (PAHs) are carcinogens produced by the thermal breakdown of organic materials. These are widely distributed in both food and the environment, and are some of the principal carcinogens in cigarette tar and air pollution. Of over 20 PAHs isolated, benzopyrene and quinoline compounds are the most commonly encountered in foods, particularly those which are broiled or fried (111). Shellfish living in petroleum contaminated waters may also contain PAHs (112).

Mutagenic PAHs have been measured in a number of cooked meats, the concentration being dependent on temperature and cooking time. Well-done meats contain more mutagenic PAHs than those cooked rare or medium rare (113, 114). Microwaving and moist-heat cooking methods produce few PAHs, presumably because of short cooking times and the lack of browning (115).

Epidemiologic studies in Japan indicate an increased risk of stomach cancer owing to consumption of broiled fish and meats (116). In the United States, stomach cancer incidence has steadily declined since the 1940s, whereas consumption of broiled food has increased (108). In addition, the average human intake of PAHs is only 0.002 of that required to produce cancer in half of animals fed. Test results are often contradictory (117) and many components of food, such as vitamin A, unsaturated fatty acids, thiols, nitrites, and even saliva itself, tend to inhibit the mutagenic activity of PAHs (118–120). Therefore, the significance of PAHs in the human diet remains unknown (121, 109).

12. Legislation and Regulatory Considerations

There exists little specific legislation dealing with natural toxicants in foods. The *1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act* stipulates that no substance that has been shown to be carcinogenic to either humans or animals may be added to the food supply. Accordingly, those foods that contain added carcinogens are subject to the Delaney Clause. Maximum tolerances of heavy metals, such as Pb and Hg, have been established by FDA at 0.5 ppm in the food product. For aflatoxins, there is presently a zero tolerance in effect (based on the Delaney Clause), and screening is generally on a qualitative basis. With these exceptions, natural toxicants in food products are generally not treated by specific food legislation (122).

Naturally occurring toxicants have been reviewed in greater detail elsewhere (22, 28, 31, 60, 61).

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Related Articles

Vitamins; Food additives; Food processing