

Food Toxicology

Steve L. Taylor

KEY CONCEPTS

- Food intoxications are caused by chemicals in foods including both synthetic and naturally occurring substances.
- The central axiom of toxicology is that all chemicals are toxic, it is the dose that makes the poison.
- Certain naturally occurring constituents (e.g. the toxins in poisonous mushrooms) and contaminants (e.g. the algal toxins causing paralytic shellfish poisoning and ciguatera poisoning) can be particularly hazardous to consumers causing serious and acute symptoms if ingested.
- Food additives do not typically elicit toxic reactions in consumers if used in accordance with governmental regulations and ingested in doses consistent with those practices.
- Lactose intolerance results from a deficiency of β -galactosidase in the small intestine so that ingestion of milk sugar or lactose elicits acute gastrointestinal complaints including flatulence, abdominal pain, and frothy diarrhea.

Food toxicology could be defined as the science that establishes the basis for judgments about the safety of foodborne chemicals. The central axiom of toxicology as set forth by Paracelsus in the 1500s states: "Everything is poison. Only the dose makes a thing not a poison." Thus, all chemicals in foods, whether natural or synthetic, inherent, adventitious, or added, are potentially toxic. The vast majority of foodborne chemicals are not hazardous because the amounts of each foodborne chemical in the typical diet are not sufficient to cause injury. The degree of risk posed by exposure to any specific foodborne chemicals is determined by the dose, duration, and frequency of exposure (and especially in the case of allergies, the degree of sensitivity of the individual). The age-old wisdom about the benefits of eating moderate amounts of a varied diet protects most consumers from any harm. Foodborne chemicals that are considered to be toxicants are those chemicals where the dose, duration, and frequency of exposure can, in at least some circumstances, be sufficient to elicit adverse reactions. Unusual diets can sometimes result in intoxications from chemicals that would normally be considered safe and desirable. For example, polar explorers experienced toxic responses to excessive intake of vitamin A as the result of consuming large amounts of polar bear liver.

Acute adverse reactions to foods can occur through many mechanisms including infections (viral, bacterial, parasitic), various intoxications, and allergies and intolerances. Food allergies are the major focus of this book. Other medical conditions including some food intoxications can cause symptoms resembling food allergies. These other conditions must be considered and eliminated in diagnosing food allergy.

Toxic reactions to food encompass all food-associated illnesses that are caused by chemicals in food, although foodborne chemicals vary greatly in toxicity. All consumers are susceptible to most food intoxications, although differences will exist primarily related to the dose of exposure and body weight (infants versus adults). Food allergy can be viewed as a category of food intoxication that affects only certain individuals in the population. Other categories of food intoxications, such as metabolic food disorders, also affect only certain individuals in the population. This chapter will focus on some of the more common types of acute foodborne intoxications including the most common metabolic food disorders. Some of the selected examples have certain manifestations in common with food allergies and intolerances and are thus of some importance in the differential diagnosis of food allergies.

Intoxications caused by synthetic chemicals in foods

Most of the synthetic chemicals in foods including food additives, agricultural chemical residues, and chemicals migrating from packaging materials have been rigorously tested

for toxicity. These synthetic chemicals are typically safe under normal circumstances of exposure, although adverse reactions can occur from misuse, either intentional or accidental. In most situations, the concentrations of chemicals in these categories are well below any levels that might be associated with adverse reactions. The focus here will be on a few intentional food additives, agricultural chemical residues, packaging migrants, and other man-made chemicals that can occur in foods at concentrations sufficient to cause concern.

Food additives

These examples were chosen because some of the manifestations are similar to symptoms that can occur during IgE-mediated allergic reactions.

Niacin

Excessive consumption of niacin (nicotinic acid), which is part of the B vitamin complex, can cause an acute onset of flushing, pruritus, rash, and burning or warmth in the skin especially on the face and upper trunk [1]. Gastrointestinal (GI) discomfort is noted by some patients. Outbreaks have sporadically occurred from the excessive enrichment of grain products as the result of inaccurate or inadequate labeling of food ingredient containers. Such episodes are rare because the amount of niacin required to elicit such symptoms is at least 50 times the recommended dietary allowance [2]. The symptoms of niacin intoxication are self-limited and without sequelae.

Sorbitol and other polyhydric alcohols

Sugar alcohols, such as sorbitol, are widely used sweeteners in dietetic food products. They are especially common in candy and chewing gum because they are non-cariogenic. Diarrhea can result from the excessive consumption of sugar alcohols [3]. Sorbitol and the other sugar alcohols are not as easily absorbed as sugar. Because of their slow absorption, these sweeteners can cause an osmotic-type diarrhea if excessive amounts are ingested. For adults, outbreaks occur from ingesting more than 20g of these sweeteners per day [3]. Infants are susceptible to lower doses. The illness is self-limited.

Toxic oil poisoning

In 1981 and 1982, an epidemic occurred in Spain linked to the ingestion of unlabeled, illegally marketed cooking oils [4]. A total of 19,828 cases and 315 deaths were recorded in this epidemic [5]. The illicit cooking oil contained oils from both plant and animal sources but some of the oils were denatured and intended for industrial rather than food uses. The causative toxin in the oils remains unknown, although fatty acid anilides resulting from the denaturation process are suspected to be at least partially responsible [5].

The clinical manifestations of this illness involved multiple organ systems [5]. In the first few days after ingestion of

the oil, patients experienced fever, chills, headache, tachycardia, cough, chest pain, and pruritus. Physical examinations revealed various skin exanthema, splenomegaly, and generalized adenopathy. Pulmonary infiltrates were noted in 84% of patients probably as the result of increased capillary permeability. The intermediate phase of the illness tended to begin in the second week and persist through the eighth week post-ingestion. GI symptoms, primarily abdominal pain, nausea, and diarrhea, predominated. Clinical examination revealed marked eosinophilia in 42% of patients, high IgE levels, thrombocytopenia, abnormal coagulation patterns, and evidence of hepatic dysfunction with abnormal enzymes. Some patients became jaundiced, and many had hepatomegaly. The late phase of the illness developed in 23% of cases and began after 2 months of illness. This phase was characterized initially by neuromuscular and joint involvement. Later, patients developed vasculitis and a scleroderma-like syndrome. Patients complained of intense muscular pain, edema, and progressive muscular weakness. Muscular atrophy was apparent in some patients. Neurological involvement included depressed deep tendon reflexes, anesthesia, and dysesthesia. Respiratory problems developed due to neuromuscular weakness and progressed to pulmonary hypertension and thromboembolic phenomena. The scleroderma-like symptoms included Raynaud's phenomenon, sicca syndrome, dysphagia, and contractures due to thickening collagen in the skin. Vascular lesions were noted in all organs apparently resulting from endothelial proliferation and thrombosis. All patients in the late group had anti-nuclear antibody and many had antibodies against smooth muscle and skeletal muscle [6]. The pathological and clinical features are consistent with an autoimmune mechanism for this illness. Since the precise causative agent and its mechanism have not been delineated, a recurrence is not impossible [5]. Also, the toxin, if present in small amounts in other foods, may be producing or aggravating other clinical conditions [5].

Agricultural chemicals

A wide diversity of chemicals are used in modern agricultural practices. Residues of these chemicals can occur in raw and processed foods, although federal regulatory agencies evaluate the use and safety of such chemicals. The major categories of agricultural chemicals would include insecticides, herbicides, fungicides, fertilizers, and veterinary drugs including antibiotics.

Insecticides

Insecticides are added to foods to control the extent of insect contamination. The major categories of insecticides include organochlorine compounds (DDT, chlordane, and others, many of which are now banned), organophosphate compounds (e.g. parathion and malathion), carbamate compounds (e.g. carbaryl and aldicarb), botanical compounds

(e.g. nicotine and pyrethrum), and inorganic compounds (e.g. arsenicals).

The exceedingly low residue levels of insecticides found in most foods are not particularly hazardous especially on an acute basis. Large doses of insecticides can be toxic to humans. For example, the organophosphates and carbamates are cholinesterase inhibitors and act as neurotoxins by blocking synaptic nerve transmission. Several reasons exist for the low degree of hazard posed by insecticide residues in foods: (i) the level of exposure is very low, (ii) some insecticides are not very toxic to humans, (iii) some insecticides decompose rapidly in the environment, and (iv) many different insecticides are used, which limits exposure to any one particular insecticide.

No food poisoning incidents have ever been attributed to the proper use of insecticides on foods. However, problems have occasionally arisen from the inappropriate use of certain insecticides [7]. An outbreak of aldicarb intoxication from watermelons occurred on the West Coast of the United States in 1985 [8]. Aldicarb use on watermelons is not allowed in the United States because excessive levels of aldicarb become concentrated in the edible portion of the melon. In this episode, several farmers used aldicarb illegally resulting in consumer illnesses and the recall and destruction of thousands of watermelons. A total of 1373 illness reports were received in this outbreak with 78% classified as probable or possible aldicarb poisoning cases [8]. This episode is thus the largest known outbreak of pesticide poisoning in North America [8]. Aldicarb has also been involved in several food poisoning outbreaks associated with ingestion of hydroponically grown cucumbers [9]. The symptoms of aldicarb intoxication include nausea, vomiting, diarrhea, and mild neurological manifestations such as dizziness, headache, blurred vision, and loss of balance [8,9]. Many other episodes of pesticide intoxications have resulted from the misuse of pesticides including contamination of foods during storage and transport, the use of pesticides in food preparation due to their mistaken identity as common food ingredients such as sugar and salt, and their misuse in agricultural practice as in the examples noted above [7].

Herbicides

Herbicides are applied to control the growth of weeds. Among the more important herbicides are chlorophenoxy compounds (e.g. 2,4-D), dinitrophenols (e.g. dinitroorthocresol), bipyridyl compounds (e.g. paraquat), substituted ureas (e.g. monuron), carbamates (e.g. protham), and triazines (e.g. simazine). Generally, herbicide residues in foods are not a hazard to consumers. No food poisoning incidents have resulted from the proper use of herbicides on food crops. The lack of hazard from herbicide residues is associated with the low level of exposure, their low degree of toxicity to humans and selective toxicity toward plants, and the use of many different herbicides which limits exposure to any particular herbicide.

Since most herbicides are selectively toxic to plants, they pose little hazard to humans in the amounts normally used for weed control. The bipyridyl compounds are an exception. These non-selective herbicides are rather toxic to humans and tend to exert their toxic effects on the lung [10]. However, no food poisoning incidents have ever been attributed to inappropriate use of the bipyridyl compounds.

Fungicides

Fungicides are used to prevent the growth of molds on food crops. Important fungicides include captan, folpet, dithiocarbamates, pentachlorophenol, and the mercurials. The hazards from foodborne fungicides are miniscule because exposure is quite low, most fungicides do not accumulate in the environment, and fungicides are typically not very toxic.

Exceptions are the mercurial compounds and hexachlorobenzene. The mercurials are often used to treat seed grains to prevent mold growth during storage. These seed grains are usually colored pink and are clearly intended for planting rather than consumption. However, on several occasions, consumers have eaten these treated seed grains and developed mercury poisoning [7]. Although some severe episodes have resulted in deaths, mild cases of mercury intoxication can be manifested in GI symptoms such as abdominal cramps, nausea, vomiting, and diarrhea, and dermal symptoms such as acrodynia and itching [7]. Hexachlorobenzene caused one of the most massive outbreaks of pesticide poisoning in recorded history affecting over 3000 individuals in Turkey from 1955 through 1959 [11]. Hexachlorobenzene-treated seed grain was consumed rather than planted resulting in severe symptoms including prophyria cutanea tarda, ulcerated skin lesions, alopecia, porphyrinuria, hepatomegaly, thyroid enlargement, and a 10% mortality rate [11].

Fertilizers

The commonly used fertilizers are combinations of nitrogen and phosphorus compounds. Nitrogen fertilizers are oxidized to nitrate and nitrite in the soil. Both nitrate and nitrite are hazardous to humans if ingested in large amounts. Infants are particularly susceptible to nitrate and nitrite intoxication. Some plants, such as spinach, can accumulate nitrate to hazardous levels if allowed to grow on overly fertilized fields. Because nitrite is more toxic than nitrate, the situation can be worsened if nitrate-reducing bacteria are allowed to proliferate on these foods.

Acute nitrite intoxications have occurred. In low doses, the symptoms include flushing of the face and extremities, GI discomfort, and headache; in larger doses, cyanosis, methemoglobinemia, nausea, vomiting, abdominal pain, collapse, and death can occur. The lethal dose of nitrite is estimated at about 1g in adults. Illnesses have occurred from ingestion of over-fertilized spinach in which bacterial

action on the nitrate-rich, unprocessed spinach allows conversion to nitrite before ingestion. Illnesses have also resulted from the improper storage of carrot juice that allowed the proliferation of nitrate-reducing bacteria resulting in the accumulation of hazardous levels of nitrite [12].

Veterinary drugs and antibiotics

Food-producing animals can be treated with a variety of veterinary drugs especially antibiotics. Residues in foods are typically quite low. Acute food poisoning incidents have not occurred as a result of properly used veterinary drugs and antibiotics. Penicillin is probably one of the major concerns because of the potential for allergic reactions to penicillin residues. However, the likelihood of allergic reactions to the very low levels of penicillin residues found in foods is quite remote [13].

Chemicals migrating from packaging materials and containers

Chemicals migrating from packaging materials into foods and beverages are not a significant source of chemical exposure. A variety of chemicals, including plastics monomers, plasticizers, stabilizers, printing inks, and others, do migrate at extremely low levels into foods. These chemicals do not often create any known hazards for consumers. Lead, copper, and tin are perhaps the main concerns associated with packaging materials. The storage of acidic foods in inappropriate containers can result in the leaching of toxic heavy metals, such as zinc. Contact of acidic beverages with copper can also release potentially hazardous levels of copper into the beverage.

Lead

Lead (Pb) exposure from foods has always been a comparatively moderate contributor to overall environmental lead exposure. The migration of Pb from Pb-soldered cans was previously a source of some concern. However, Pb-soldered cans have been successfully phased out of use in the United States. The main issue with Pb contamination remains the occasional use of Pb-based glazes on pottery or paint on glassware that may come in contact with acidic foods or beverages. Pb is a well-known toxicant that can affect the nervous system, the kidney, and the bone.

Tin

Tin plate is commonly used in the construction of metal cans for foods. The inner surfaces of these cans are lined with a lacquer material when cans are used for acidic foods or beverages. Acute tin intoxication has occurred from the inappropriate placement of tomato juice or fruit cocktail in unlined cans. Since tin is poorly absorbed, the primary symptoms are bloating, nausea, abdominal cramps, vomiting, diarrhea, and headache occurring 30 minutes to 2 hours after consumption of the acidic product.

Copper

Copper poisoning, characterized primarily by nausea and vomiting, most commonly occurs from faulty check valves in soft drink vending machines. The check valves prevent contact between the acidic, carbonated beverage, and the copper tubing that delivers the water or ice in the machine. Several outbreaks of copper poisoning have resulted from such occurrences. Copper poisoning results in acute gastroenteritis.

Zinc

Zinc intoxication typically results from the unwise storage of acidic foods or beverages in galvanized containers. Zinc is a potent emetic. The symptoms of zinc intoxication include irritation of the mouth, throat, and abdomen; nausea and vomiting; dizziness; and collapse.

Industrial chemicals

Industrial and/or environmental pollutants often migrate into foods in small amounts. On rare occasions, hazardous levels of such chemicals enter the food supply often with devastating consequences.

Polychlorinated biphenyls and polybrominated biphenyls

The contamination of foods with polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) has occurred on several occasions. PCBs and PBBs are quite persistent in the environment and are considered to be toxic pollutants from industrial practices. PBBs are commonly used as fire retardants, while PCBs are frequently used in transformer fluid. PCBs and PBBs are not worrisome acute toxicants in foods. However, since they are lipid-soluble, the chronic effects of exposure to these contaminants in foods are of concern. The most infamous incident involved the accidental contamination of dairy feed in Michigan with PBBs. This incident resulted in the destruction of many cows and their milk. Leaking transformers have contributed to the contamination of feeds with PCBs which led to the destruction of chickens, eggs, and egg-containing food products.

Mercury

Minamata disease, due to mercury (Hg) intoxication, is the classic example of the contamination of foods by industrial pollutants [14]. An industrial firm located on the shores of Minamata Bay in Japan dumped Hg-containing wastes into the bay where bacteria converted the inorganic Hg into highly toxic methylmercury. Fish in the bay became contaminated with the methylmercury. Over 1200 cases of Hg intoxication occurred among consumers of Minamata Bay fish [14]. The symptoms included tremors and other neurotoxic effects and kidney failure.

Intoxications caused by naturally occurring chemicals in foods

The naturally occurring chemicals in foods are less frequently tested for their potential toxic effects than synthetic chemicals. While the vast majority of naturally occurring chemicals in foods are safe under the normal circumstances of exposure, some potentially hazardous situations do exist. Those naturally occurring chemicals with significant pharmacological activity including the vasoactive amines, methylxanthines, ethanol, and myristicin are covered elsewhere. However, naturally occurring chemicals in foods can elicit a wide variety of adverse reactions including both acute and chronic intoxication. Naturally occurring toxicants could be defined as those naturally occurring chemicals in foods that might be hazardous under typical circumstances of exposure. Naturally occurring chemicals in foods are more likely to be hazardous under typical circumstances of exposure than are synthetic chemicals. Although chronic illnesses, such as cancer, are undeniably important, this chapter will focus exclusively on acute intoxications caused by natural, foodborne toxicants.

Naturally occurring contaminants

Naturally occurring contaminants can be produced in foods as the result of contamination by bacteria, molds, algae, and insects. The chemicals produced from these biological sources can remain in foods even after the living organism has been removed or destroyed. Naturally occurring contaminants are not always present in foods and can be avoided, if contamination is prevented. Such contaminants represent the most important and potentially hazardous chemicals of natural origin existing in foods. The bacterial and insect toxins will not be discussed in detail. The bacterial toxins cause very familiar diseases including staphylococcal food poisoning and botulism. The insect toxins have not been studied to any extent, and their impact on human health is uncertain.

The toxicants produced by algal species that bioaccumulate in seafoods are among the most common causes of foodborne illness of chemical etiology. These algal toxicants are involved with several of the seafood poisonings including ciguatera poisoning and paralytic shellfish poisoning. Mycotoxins produced by foodborne molds are a source of considerable toxicological concern and occur at low levels rather frequently in certain stored foods. Several of the mycotoxins will be discussed in some detail because they are confirmed to be involved in acute foodborne illness. A bigger concern with the mycotoxins is their potential involvement with chronic toxicity. The chronic toxicity of mycotoxins will not be described here because it is unlikely to be relevant to the investigation of allergic reactions.

Ciguatera poisoning

Ciguatera poisoning results from the ingestion of fish that have fed on toxic dinoflagellate algae. Ciguatera

poisoning is the most common cause of acute foodborne disease of chemical etiology reported to the Centers for Disease Control. This foodborne illness is common throughout the Caribbean, South Pacific, and Indian Ocean areas, but is now encountered around the world due to the improved distribution of fish [15,16]. In the United States, the illness occurs most frequently in Florida, Hawaii, and the Virgin Islands. The fish most commonly implicated in cases of ciguatera poisoning are large tropical and semi-tropical reef fishes such as grouper, barracuda, sea bass, Spanish mackerel, snappers, and sea perches, although as many as 400 different fish species have been implicated in this illness. Curiously, although most cases involve tropical or semi-tropical fishes, at least one outbreak has involved farm-raised salmon [17].

With the tropical and semi-tropical reef fishes, the fish acquire the toxic agent(s) by feeding on smaller fishes that acquire the toxin from the poisonous planktonic algae [16]. Several species of dinoflagellate algae appear able to produce toxins of the type associated with ciguatera poisoning; *Gambierdiscus toxicus* is one of the most prominent [16]. Several toxins may be involved in ciguatera poisoning [16,18]. The major toxins, known as ciguatoxins, are lipid-soluble, heat-stable, polyether compounds with an approximate molecular weight of 1110 Da [16,18]. Ciguatoxin has ionophoric properties, which selectively opens voltage-sensitive sodium channels of the neuromuscular junction. Maitotoxin also appears to be responsible to a lesser extent for ciguatera poisoning [16,18]. Maitotoxin is a water-soluble compound of molecular weight of 3424 Da which activates both voltage-sensitive and receptor-operated calcium channels in the plasma membranes of cells. The toxins accumulate in the liver and viscera of the fish, but enough can enter the muscle tissues to result in ciguatera poisoning among humans ingesting these fish [16]. Larger fish pose a greater risk than smaller fish. The toxins are heat-stable and are unaffected by processing or cooking practices.

The symptoms of ciguatera poisoning tend to be somewhat variable perhaps confirming the role of several different dinoflagellate algae and several different toxins in this syndrome [15,16]. GI and neurological manifestations are the predominant symptoms associated with ciguatera poisoning, although in some cases, the GI symptoms predominate, while in other cases, the neurological symptoms predominate. The GI symptoms include nausea, vomiting, diarrhea, and abdominal cramps. The neurological symptoms include dysesthesia, paresthesia especially in the perioral region and extremities, pruritus, vertigo, muscle weakness, malaise, headache, and myalgia. A peculiar reversal of hot and cold sensations occurs in about 65% of all patients [18]. In severe cases, the neurological manifestations can progress to delirium, pruritus, dyspnea, prostration, bradycardia, and coma [18]. Many patients recover within a few days or weeks, although treatment is difficult and deaths

from cardiovascular collapse have been encountered in about 0.1% of cases [19].

Paralytic shellfish poisoning

Paralytic shellfish poisoning results from the ingestion of molluscan shellfish, such as clams, mussels, cockles, and scallops, that have become poisonous by feeding on toxic dinoflagellate algae [15,20]. Paralytic shellfish poisoning occurs worldwide but is commonly encountered along the Pacific and North Atlantic coasts of North America, the coastal areas of Japan, and the coasts of Chile and Argentina [16]. Several species of toxic dinoflagellate algae have been implicated in paralytic shellfish poisoning; *Alexandrium catenella* (formerly *Gonyaulax catenella*) and *A. tamarensis* are two of the most common ones. "Blooms" of the toxic dinoflagellates are sporadic, so most shellfish will be hazardous only during the times of the blooms. While most shellfish species clear the toxins from their system within a few weeks after the end of the dinoflagellate bloom, a few species, such as the Alaskan butter clam, seem to retain the toxin for long periods [21]. The toxins involved in paralytic shellfish poisoning are known as saxitoxins [22]. Saxitoxins are neurotoxins that bind to and block the sodium channels in nerve membranes [16]. The saxitoxins are heat-stable so processing and cooking have no effect on the toxicity of the shellfish.

Through the blocking of nerve transmission, the saxitoxins are very potent neurotoxins. The symptoms of paralytic shellfish poisoning include a tingling sensation and numbness of the lips, tongue, and fingertips followed by numbness in the legs, arms, and neck, ataxia, giddiness, staggering, drowsiness, incoherent speech progressing to aphasia, rash, fever, and respiratory and muscular paralysis [15,16]. Death from respiratory failure occurs frequently, usually within 2–12 hours depending on the dose ingested. No antidotes are known, although prognosis is good if the victim survives the first 24 hours of the illness.

Amnesic shellfish poisoning

Amnesic shellfish poisoning was first recognized following an outbreak in Canada in late 1987 [23]. Amnesic shellfish poisoning was associated with the ingestion of mussels from Prince Edward Island which resulted in over 100 cases and at least four deaths [23,24]. The source of the toxin was a planktonic algae, *Nitzschia pungens*, which was blooming in an isolated area of Prince Edward Island at the time of the outbreak [25]. The toxin involved was identified as domoic acid, a neuroexcitatory amino acid [24]. Amnesic shellfish poisoning is characterized by GI symptoms and unusual neurological abnormalities [24]. The GI symptoms, which occurred within the first 24 hours, were vomiting, abdominal cramps, and diarrhea. The neurological symptoms, which had onset within 48 hours, were severe incapacitating headaches, confusion, loss of short-term memory, and, in a few cases, seizures and coma. Severely affected patients

who did not die experienced prolonged neurologic sequelae including memory deficits and motor or sensorimotor neuropathy or axonopathy [24].

Diarrhetic shellfish poisoning

Diarrhetic shellfish poisoning is primarily associated with the ingestion of clams that have become toxic through the ingestion of toxic dinoflagellate algae of the genus *Dinophysis* and *Prorocentrum* [16]. No confirmed outbreaks have occurred in North America but outbreaks have occurred primarily in Japan and Europe [19]. The toxins responsible for diarrhetic shellfish poisoning are polyether compounds: okadaic acid and its derivatives, the dinophysistoxins [16]. The symptoms include diarrhea, nausea, vomiting, and abdominal cramps [19].

Pufferfish poisoning

Pufferfish poisoning occurs primarily in Japan and China, the only parts of the world where pufferfish are frequently consumed. While about 30 species of pufferfish are found worldwide, most species are not toxic. The most hazardous pufferfish belong to the genus *Fugu*, which are considered in Japan and China to be delicacies. The toxin in pufferfish is a potent neurotoxin called tetrodotoxin [26]. For many years, the toxin was thought to be produced by the fish, but evidence now exists that marine bacteria may be the original source of the toxin [27]. Tetrodotoxin is heat-stable and, like saxitoxin, acts by blocking the sodium channels in nerve cell membranes. The symptoms of tetrodotoxin poisoning usually begin with a tingling sensation of the fingers, toes, lips, and tongue, followed by nausea, vomiting, diarrhea, and epigastric pain [26]. Twitching, tremors, ataxia, paralysis, and death often ensue [26]. The fatality rate is about 60% in untreated cases. Most of the tetrodotoxin accumulates in the liver, viscera, and roe of the pufferfish. Careful cleaning of the fish, before ingestion of the edible muscle, is required to safeguard against tetrodotoxin intoxication.

Mycotoxins

Mycotoxins are produced by a wide variety of molds which can grow and produce toxins on a wide variety of foods [28]. Most of the known mycotoxins have been recognized because of their toxicity to domestic animals fed moldy feed grains. However, a few mycotoxins are noteworthy because they are known hazards for humans.

Ergotism

Ergotism was the first recognized mycotoxin-associated illness. The responsible mold is *Claviceps purpurea*, which can infect the grains of rye, wheat, barley, and oats. The last recorded outbreak of ergotism occurred in Europe in 1951. Ergotism is caused by a group of toxins known as the ergot alkaloids. Ergotism is manifested in two forms: gangrenous ergotism and convulsive ergotism. Gangrenous ergotism, also

known as Saint Anthony's fire, is characterized by a burning sensation in the feet and hands followed by progressive restriction of blood flow to the hands and feet resulting ultimately in gangrene and loss of limbs. Convulsive ergotism is characterized by hallucinations leading to convulsive seizures and sometimes death. Modern agricultural practices and grain milling procedures have virtually eliminated ergotism as a concern.

Alimentary toxic aleukia

Alimentary toxic aleukia (ALA) was observed in Russia during World War II and was associated with the consumption of over-wintered millet that contained trichothecene mycotoxins. Trichothecenes are a group of mycotoxins produced by molds of the genus *Fusarium*. ALA occurs in four stages. In the first stage, affected individuals experience burning sensations in the mouth, throat, and esophagus followed 1–3 days later by diarrhea, nausea, and vomiting. The GI symptoms cease after about 9 days. The second stage of ALA begins during the second week and lasts through the second month. This stage involves bone marrow destruction, leukemia, agranulocytosis, anemia, and loss of platelets. Small hemorrhages begin to appear at the end of this stage. The third stage of ALA lasts for 5–20 days and involves total loss of bone marrow with necrotic angina, sepsis, total agranulocytosis, moderate fever, larger hemorrhages on the skin, and the appearance of necrotic skin lesions. Bronchial pneumonia usually develops along with abscesses and hemorrhages in the lungs. The fourth stage of ALA is death, which occurred in about 80% of cases within 3 months of the onset of symptoms. Due to the circumstances at the time of this outbreak, the identification of the exact species of *Fusarium* and the trichothecenes responsible for ALA were not accomplished. The level of contamination of the millet with trichothecenes was not determined.

Fusarium molds are very common on grain crops worldwide. Trichothecene mycotoxins continue to occur at low levels in many cereal foods. However, no acute illnesses in humans including ALA have been attributed to trichothecene intoxication since the original outbreak. The effects of ingestion of low levels of toxic trichothecenes on humans remain uncertain.

Naturally occurring constituents

Many fungi, some plants, and a few animals contain hazardous levels of various naturally occurring toxicants. Such fungi, plants, and animals should not be eaten, but are accidentally or intentionally consumed on occasion resulting in foodborne illness. Furthermore, many plants and animals contain levels of naturally occurring toxicants that are probably not hazardous to humans ingesting typical amounts of these foods. The ingestion of abnormally large quantities of such foods and their naturally occurring toxicants is potentially hazardous. Some naturally occurring toxicants are inactivated or removed

during processing or preparation of foods prior to consumption. The failure to adhere to such processing and preparation practices can result in foodborne illness.

Poisonous animals

Very few animal species are poisonous, although several species of poisonous fish and other marine animals are known to exist. Pufferfish is the best-known example, although the toxin in pufferfish may actually emanate from bacteria [27].

Animal tissues and products also contain very few naturally occurring toxicants that could cause adverse reactions if ingested in abnormally large quantities. Fat-soluble vitamins, most notably vitamin A, serve as an example. Cases of vitamin A intoxication have occurred in polar explorers ingesting polar bear liver and in infants resulting from feeding diets rich in vitamin A (e.g. chicken livers and fortified milk) and carotenoids (e.g. pureed carrots), while also administering daily vitamin supplements [29].

Poisonous plants

Many poisonous plants exist in nature [30]. Classic examples would include water hemlock and nightshade which were used in centuries past to poison one's enemies. While consumers purchasing foods from commercial sources can usually avoid the ingestion of poisonous plants, intoxications occur among individuals who have harvested their own foods in the wild. For example, an elderly couple succumbed after mistaking foxglove for comfrey while harvesting herbs for tea; foxglove contains digitalis. In another example, a team member in a desert survival course died after eating a salad prepared in part from a *Datura* species, jimsonweed. Jimsonweed contains tropane alkaloids including atropine. While atropine is a useful pharmaceutical agent, its ingestion from natural sources in uncontrolled doses can be fatal. Atropine has potent anticholinergic properties, and individuals ingesting jimsonweed and other plants containing tropane alkaloids suffer neurotoxic effects. Many more such examples could be provided.

More rarely, intoxications from poisonous plants occur with products purchased from commercial sources. In one well-investigated outbreak, a commercial herbal tea was contaminated with *Senecio longilobis*, a well-known poisonous plant [31]. The herbal tea, called gordolobo yerba, was sold to the Mexican-American population in Arizona, and promoted as a cure for colic, viral infections, and nasal congestion in infants. Several infants died from the ingestion of this contaminated herbal tea. *Senecio* and many other plants contain a group of chemicals known as pyrrolizidine alkaloids. The pyrrolizidine alkaloids can cause both acute and chronic symptoms. Chronic low doses produce liver cancer and cirrhosis. The acute symptoms associated with the contaminated herbal tea included ascites, hepatomegaly, veno-occlusive liver disease, abdominal pain, nausea, vomiting, headache, and diarrhea [31]. Death resulted from liver failure.

Occasionally, intoxications from poisonous plants occur from the intentional addition of such materials to foods. The intentional addition of marijuana to bakery items is the most common example.

Many plant-derived foods contain naturally occurring toxicants at doses that are not hazardous, at least on an acute basis, unless large quantities of the food are eaten. Examples would include solanine and chaconine in potatoes, oxalates in spinach and rhubarb, furan compounds in mold-damaged sweet potatoes, and cyanogenic glycosides in lima beans, cassava, and many fruit pits [32].

The cyanogenic glycosides, for example, can release cyanide from enzymatic action occurring during the storage and processing of the foods, or on contact with stomach acid. Commercial varieties of lima beans contain minimal amounts of these cyanogenic glycosides having a hydrogen cyanide (HCN) yield of 10 mg per 100 g of lima beans (wet weight). The lethal oral dose of cyanide for humans is 0.5 mg/kg, so a 70-kg adult would need to ingest 35 mg of cyanide, an amount that would require the ingestion of at least 350 g of lima beans. Such levels of consumption are quite unlikely, and human illnesses from cyanide intoxication from lima bean ingestion have not been reported. Wild varieties of lima beans contain much higher levels of the cyanogenic glycosides (up to 300 mg HCN/100 g) and would likely be hazardous to consume. Cyanide intoxications have occurred in Africa and South America due to the consumption of cassava which is sometimes ingested in large quantities due to a lack of other foods [32]. Cyanide intoxication has also occurred from the ingestion of fruit pits, especially by the grinding of pits with the fruit in food processors during the preparation of jams and wines. The symptoms of cyanide intoxication include a rapid onset of peripheral numbness and dizziness, mental confusion, stupor, cyanosis, twitching, convulsions, coma, and death.

Many toxic constituents of plants are inactivated or removed during processing and preparation. For example, raw soybeans contain trypsin inhibitors, lectins, amylase inhibitors, saponins, and various antivitamin. Fortunately, these toxicants are inactivated during the heating and fermentation processes used with soybeans. Failure to remove or inactivate these toxicants can result in foodborne illness. For example, raw kidney beans contain lectins which are typically inactivated during cooking. In the United Kingdom, immigrants who did not appreciate the importance of thorough cooking of kidney beans have ingested undercooked kidney beans leading to the onset of nausea, vomiting, abdominal pain, and bloody diarrhea from the lectins.

Poisonous mushrooms

Many species of mushrooms are poisonous. The harvesting of mushrooms in the wild can be a hazardous practice. Intoxications occur each year in the United States from the ingestion of poisonous mushrooms. Poisonous mushrooms

contain a variety of naturally occurring toxicants which can be classified into Groups I–VI [33].

The Group I toxins are the most hazardous and include amatoxin and phallotoxin. Amatoxin is produced by *Amanita phalloides*, the death cap mushroom. Amatoxin poisoning occurs in three stages. The first stage involves abdominal pain, nausea, vomiting, diarrhea, and hyperglycemia beginning 6–24 hours after ingestion of the mushrooms. A short period of remission then occurs. The third and often fatal stage involves severe liver and kidney dysfunction, hypoglycemia, convulsions, coma, and death. Death resulting from hypoglycemic shock occurs 4–7 days after the onset of symptoms.

The Group II toxins are hydrazines; gyromitrin is the best-known example. Gyromitrin is produced by *Gyromitra esculenta* or false morel mushrooms. The symptoms elicited by ingestion of these mushrooms include a bloated feeling, nausea, vomiting, watery or bloody diarrhea, abdominal pain, muscle cramps, faintness, and ataxia occurring with a 6–12 hour onset time.

The Group III toxins are characterized by muscarine and affect the autonomic nervous system. Muscarine is found in fly agaric (*Amanita muscaria*) sometimes in association with the Group I toxins. Symptoms include perspiration, salivation, lacrimation with blurred vision, abdominal cramps, watery diarrhea, constriction of the pupils, hypotension, and a slowed pulse occurring rapidly following the ingestion of the poisonous mushrooms.

The Group IV toxins cause symptoms only when ingested with alcoholic beverages. Coprine, a Group IV toxin produced by *Coprinus atramentarius*, is the best example. Symptoms include flushing of the neck and face, distension of the veins in the neck, swelling and tingling of the hands, metallic taste, tachycardia, and hypotension progressing to nausea and vomiting. Symptoms begin within 30 minutes of ingestion of the mushrooms and can last for up to 5 days.

The Group V and VI toxins act primarily on the central nervous system causing hallucinations. The Group V toxins include ibotenic acid and muscimol and cause dizziness, drowsiness followed by hyperkinetic activity, confusion, delirium, incoordination, staggering, muscular spasms, partial amnesia, a coma-like sleep, and hallucinations beginning 30 minutes to 2 hours after ingestion. Fly agaric is a good source of the Group V toxins.

The Group VI toxins include psilocybin and psilocin. The symptoms of the Group VI toxins include pleasant or aggressive mood, anxiety, unmotivated laughter and hilarity, compulsive movements, muscle weakness, drowsiness, hallucinations, and sleep. The Group VI toxins are found in Mexican mushrooms, *Psilocybe mexicana*. Symptoms usually begin 30–60 minutes after ingestion of the mushrooms, and recovery is often spontaneous in 5–10 hours. When the dose of the Group VI toxins is high, prolonged and severe sequelae, even death, can occur.

Metabolic food disorders

Like food allergies, metabolic food disorders affect only certain individuals in the population. These individuals display increased sensitivity to certain chemicals in foods because they lack an enzyme necessary to metabolize that particular chemical or because they have a genetic abnormality that makes them especially susceptible to the toxic effects of a particular foodborne chemical. The best examples of metabolic food disorders are lactose intolerance and favism.

Lactose intolerance

Lactose intolerance is associated with an inherited deficiency in the amount of the enzyme, β -galactosidase, in the small intestine [34]. β -galactosidase is needed for the hydrolysis of the milk disaccharide, lactose, into its constituent monosaccharides, glucose and galactose. While glucose and galactose can be absorbed and used for metabolic energy, lactose cannot be absorbed without prior hydrolysis. If the activity of β -galactosidase is insufficient, the lactose from milk or dairy products will be incompletely hydrolyzed. Undigested lactose will pass into the colon where the large numbers of bacteria will convert it to CO_2 , H_2 , and H_2O . The symptoms associated with lactose intolerance are abdominal cramps, flatulence, and frothy diarrhea.

Almost all individuals are born with sufficient levels of β -galactosidase activity. However, with increasing age, the levels of enzyme activity diminish. At some point, the levels of β -galactosidase activity may be insufficient to handle the load of lactose ingested in the diet. Symptoms of lactose intolerance can begin to appear in the early teen years and often worsen with advancing age. Many lactose-intolerant individuals can tolerate some lactose in their diets, often as much as the amount found in an 8-oz glass of milk [35]. The degree of tolerance may lessen with advancing age.

Lactose intolerance is an inherited trait. It affects only about 6–12% of all Caucasians, but ultimately affects 60–90% of some ethnic groups including black Americans, Native Americans, Hispanics, Asians, Jews, and Arabs [34].

Lactose intolerance is treated with dairy product avoidance diets, although some dairy products can usually be ingested without harm. Lactose-intolerant individuals can often safely consume yogurt if the yogurt contains live bacterial cultures with β -galactosidase [34]. Lactose-hydrolyzed milk is also available in many markets.

Favism

Favism is caused by the ingestion of fava beans or the inhalation of pollen from the *Vicia faba* plant by individuals with a deficiency of the enzyme, glucose-6-phosphate dehydrogenase (G6PDH), in their erythrocytes [36]. Erythrocyte G6PDH deficiency is the most common enzyme deficiency in the world, affecting perhaps 100 million individuals. Erythrocyte G6PDH deficiency is most prevalent among Kurds, Iraqis, Iranians, Sardinians, Cypriot Greeks,

American blacks, and some African populations. This deficiency is virtually unknown in northern Europeans, North American Indians, and Eskimos. G6PDH is a critical enzyme which is essential for the maintenance of adequate levels of the reduced form of glutathione (GSH) and nicotinamide dinucleotide phosphate (NADPH) in erythrocytes. GSH and NADPH protect the erythrocyte membrane from oxidation. Fava beans contain two potent, naturally occurring oxidants, vicine and convicine. These oxidants can damage the erythrocyte membranes in G6PDH-deficient individuals, but not normal persons. Exposure to fava beans in sensitive individuals results in acute hemolytic anemia. The typical symptoms are pallor, fatigue, dyspnea, nausea, abdominal and/or back pain, fever, and chills. In a few severe cases, hemoglobinuria, jaundice, and renal failure may occur. Favism is not a common malady in the United States because fava beans are rarely ingested here. Favism occurs primarily in the Mediterranean area, the Middle East, China, and Bulgaria where the genetic trait is fairly prevalent and fava beans are more frequently consumed.

References

- 1 Press E, Yeager L. Food "poisoning" due to sodium nicotinate – report of an outbreak and a review of the literature. *Am J Public Health* 1962;52:1720–8.
- 2 Burkhalter J, Shore M, Wollstadt L, *et al.* Illness associated with high levels of niacin in cornmeal – Illinois. *CDC MMWR* 1981;30:11–12.
- 3 Taylor SL, Byron B. Probable case of sorbitol-induced diarrhea. *J Food Prot* 1984;47:249.
- 4 Kilbourne EM, Rigau-Perez JG, Heath Jr CW, *et al.* Clinical epidemiology of toxic oil syndrome: manifestations of a new illness. *N Engl J Med* 1983;309:1408–14.
- 5 Condemni JJ. Unusual presentations. In: Frieri M, Kettelhut B (eds.) *Food Hypersensitivity and Adverse Reactions – a Practical Guide to Diagnosis and Management*. New York: Marcel Dekker, 1999: 331–46.
- 6 Rodriguez M, Nogura AE, Del Villaras S, *et al.* Toxic synovitis from denatured rapeseed oil. *Arthritis Rheum* 1982;25: 1477–80.
- 7 Ferrer A, Cabral R. Toxic epidemics caused by alimentary exposure to pesticides. *Food Addit Contam* 1991;8:755–76.
- 8 Goldman LR, Beller M, Jackson RL. Aldicarb food poisonings in California, 1985–1988; toxicity estimates for humans. *Arch Environ Health* 1990;45:141–7.
- 9 Goes EA, Savage EP, Gibbons G, *et al.* Suspected foodborne carbamate pesticide intoxication associated with ingestion of hydroponic cucumbers. *Am J Epidemiol* 1980;111:254–60.
- 10 Taylor SL, Nordlee JA, Kapels LM. Foodborne toxicants affecting the lung. *Pediatr Allergy Immunol* 1991;3:180–7.
- 11 Schmid R. Cutaneous porphyria in Turkey. *N Engl J Med* 1960; 268:397–8.

- 12 Keating JP, Lell ME, Straus AW, *et al.* Infantile methemoglobinemia caused by carrot juice. *N Engl J Med* 1973;288:825–6.
- 13 Dewdney JM, Edwards RG. Penicillin hypersensitivity – Is milk a significant hazard? A review. *J Royal Soc Med* 1984;77:866–77.
- 14 Kurland LT, Faro SN, Siedler H. Minamata disease. *World Neurol* 1960;1:370–95.
- 15 Isbister GK, Kiernan MC. Neurotoxic marine poisoning. *Lancet Neurol* 2005;4:219–28.
- 16 Whittle K, Gallacher S. Marine toxins. *Br Med Bull* 2000;56:236–53.
- 17 DiNubile MJ, Hokama Y. The ciguatera poisoning syndrome from farm-raised salmon. *Ann Intern Med* 1995;122:113–14.
- 18 Russell FE, Egen NB. Ciguatoxic fishes, ciguatoxin (CTX) and ciguatera poisoning. *J Toxicol Toxin Revs* 1991;10:37–62.
- 19 Mines D, Stahmer S, Shephard SM. Poisonings – food, fish, shellfish. *Emerg Clin North Am* 1997;13:157–77.
- 20 Lipp EK, Rose JB. The role of seafood in foodborne disease in the United States of America. *Rev Sci Tech* 1997;16:620–33.
- 21 Gessner BD, Middaugh JP. Paralytic shellfish poisoning in Alaska: a 20-year retrospective analysis. *Am J Epidemiol* 1995;141:766–70.
- 22 Okada K, Niwa M. Marine toxins implicated in food poisoning. *J Toxicol Toxin Revs* 1998;17:373–84.
- 23 Perl TM, Bedard L, Kosatsky T, *et al.* An outbreak of toxic encephalopathy caused by eating mussels contaminated with domoic acid. *N Engl J Med* 1990;322:1775–80.
- 24 Todd ECD. Domoic acid and amnesic shellfish poisoning – a review. *J Food Prot* 1993;56:69–83.
- 25 Bates SS, Bird CJ, DeFreitas ASW, *et al.* Pennate diatom *Nitzschia pungens* as the primary source of domoic acid, a toxin in shellfish from eastern Prince Edward Island, Canada. *Can J Fish Aquatic Sci* 1989;46:1203–15.
- 26 Noguchi T, Ebesu JSM. Puffer poisoning: epidemiology and treatment. *J Toxicol Toxin Rev* 2001;20:1–10.
- 27 Miyazawa K, Noguchi T. Distribution and origin of tetrodotoxin. *J Toxicol Toxin Rev* 2001;20:11–33.
- 28 Van Genderen H. Adverse effects of naturally occurring nonnutritive substances. In: deVries J (ed.) *Food Safety and Toxicology*. Boca Raton, FL: CRC Press, 1997:147–62.
- 29 Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes – A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients*. Washington, DC: National Academy Press, 1998.
- 30 Smith RA. Poisonous plants. In: Hui YH, Gorham JR, Murrell KD, Cliver DO (eds.) *Foodborne Disease Handbook. Vol. 3. Diseases Caused by Hazardous Substances*. New York: Marcel Dekker, 1994:187–226.
- 31 Huxtable RJ. Herbal teas and toxins: novel aspects of pyrrolizidine poisoning in the United States. *Perspect Biol Med* 1980;24:1–14.
- 32 Beier RC, Nigg HN. Toxicology of naturally occurring chemicals in foods. In: Hui YH, Gorham JR, Murrell KD, Cliver DO (eds.) *Foodborne Disease Handbook. Vol. 3. Diseases Caused by Hazardous Substances*. New York: Marcel Dekker, 1994:1–186.
- 33 Spoerke Jr DG. Mushrooms: epidemiology and medical management. In: Hui YH, Gorham JR, Murrell KD, Cliver DO (eds.) *Foodborne Disease Handbook. Vol. 3. Diseases Caused by Hazardous Substances*. New York: Marcel Dekker, 1994:433–62.
- 34 Stear GIJ, Horsburgh K, Steinman HA. Lactose intolerance – a review. *Curr Allergy Clin Immunol* 2005;18:114–19.
- 35 Lisker R, Aguilar L. Double blind study of milk lactose intolerance. *Gastroenterology* 1978;74:1283–5.
- 36 Marquardt RR, Wang N, Arbid MS. Pyrimidine glycosides. In: D’Mello JPF (ed.) *Handbook of Plant and Fungal Toxicants*. Boca Raton, FL: CRC Press, 1997:139–55.